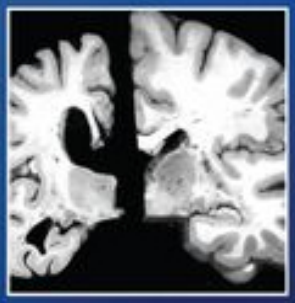
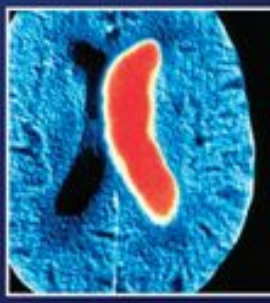
EDITORS
Alan J. Sinclair, John E. Morley
and Bruno Vellas

FIFTH EDITION

PATHY'S PRINCIPLES AND PRACTICE OF GERIATRIC MEDICINE



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To my mother, Ivy, and father, Radovan, for giving me the opportunity.

–Alan J. Sinclair

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

–John E. Morley

To all the teams working at the Gérontopôle, to my father Professor Pierre Vellas who created the Universities of the Third Age, and to Professor J.L. Albarede, our mentor.

–Bruno Vellas

Pathy's Principles and Practice of Geriatric Medicine

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FIFTH EDITION

Volume 1

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Preface to the Fourth Edition

> ''I offer no apology for the publication of this volume. The subject is one of the highest importance, and yet it has been strangely overlooked during the last half-century by the physicians of all countries.''
>
> –George Edward Day
> (1815–1872)

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

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

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

The general outline of the text still follows that of the first edition. The first sections provide a general perspective of old age, the processes of aging, and social and community perspectives. The chapter on preventive medicine now focuses on issues of particular importance to older persons. In Part III ''Medicine in Old Age'', the section ''Eating Disorders and Nutritional Health'' has been increased to recognize the increased importance and understanding of nutrition in old age. Chapters on frailty, sarcopenia,

palliative care, and women's health have been added to recognize the increasing importance of these issues in older persons. The final part on ''Health Care Systems'' focuses first on the emergence of continuous quality improvement, geriatric systems and evidence-based medicine as the foundation of high-quality geriatric medicine. The development of novel education systems is discussed. Finally, unique aspects of geriatric care around the world are examined.

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

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

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

Preface to the Fifth Edition

The Fifth Edition of this widely known international textbook incorporates the latest evidence of research into the often complex management of common clinical problems in older people. We as Editors embarked on this edition with the knowledge that John Pathy would be there to guide us with all his wisdom and incredible grasp of the discipline of Geriatric Medicine. His untimely departure from this world left a major gap for us, but we have worked very closely as an editorial team, supported by Wiley-Blackwell, and hope that this edition fulfils all the expectations and objectives that were set when we originally sat down with John Pathy to discuss the textbook. We pay tribute to John Pathy as a tremendous role model for aspiring geriatricians all over the world and hope that his textbook will continue to educate all those who seek enlightenment in caring for older people.

We have used, wherever possible, an evidence-based approach to developing each chapter and asked all authors to think hard on what are the key messages. Chapters that have been revised and updated were edited closely to ensure that the clinical pathway is still highly relevant and that the references also reflected an in-depth revision process. A new layout of chapters will be apparent and is based on grouping chapters with similar clinical relevance and where similar pathophysiological mechanisms may be operating. In a majority of chapters, we have leading international authors who are experts in the field.

Wide clinical experience is the hallmark of a sound geriatrician or other healthcare specialist who claims expertise in managing older people who are hospitalized or who have clinically deteriorated in the community. This may take many years of training, although at an early stage of their careers, recognition of the varying nature of illness in old age and how both simple and focused interventions can lead to health gain are prerequisites for enhancing clinical care. This textbook should complement these activities irrespective of the status of the practitioner but, as always, reading a book and acquiring knowledge must be accompanied by a practical clinical care approach aligned with compassion and understanding of the critical issues affecting older people.

Professor Alan Sinclair would like to thank Caroline Sinclair, and Professor John Morley would like to thank Susan Brooks, for their tremendous assistance in helping them to complete their editorial tasks, and the Editors would like to express their appreciation of the incredible patience and support from Gill Whitley and Robyn Lyons at Wiley-Blackwell.

Alan J. Sinclair
John E. Morley
Bruno Vellas

Foreword

One of my earliest memories is of my father at work in his small study: he would be surrounded by what, to a child's eye, appeared to be a chaotic mass of books, journals, papers and slides. He never seemed to rest. The time not occupied by professional work was filled with hard labour in the garden or, with the constant support of his devoted wife Norma, in bringing up five children.

One of the results of the drive and determination in that time spent in his study was the first edition of *Principles and Practice of Geriatric Medicine* in 1985. I had become a medical student by that time, and remember the work involved in the production of that first edition. Twenty-five years on, I wonder at how my father managed to find the time, after completion of all his clinical and teaching tasks, even to contemplate such a *magnum opus* – however, many distinguished contributors may have been ready to assist.

The success of the first edition led to a request for a second, enlarged, edition, and then to a third edition. It was during the production of the third edition that my father himself required in-patient treatment. During this stay in hospital I called in to visit him, but found that he was not in bed but in the ward office on the telephone to a consultant at the hospital who was a contributor to the book, simply confirming that the contribution would be received by the deadline.

My father died before he could begin work himself on the fifth edition. Although by then he was no longer as physically fit as he would have wished, particularly for gardening, he remained mentally sharp, alert and energetic. Medicine remained his passion. He continued to be involved in research and remained abreast of the latest developments in professional literature. His private study, where he continued to beaver away energetically, remained as chaotic as ever.

Dr Damian Pathy FRCP

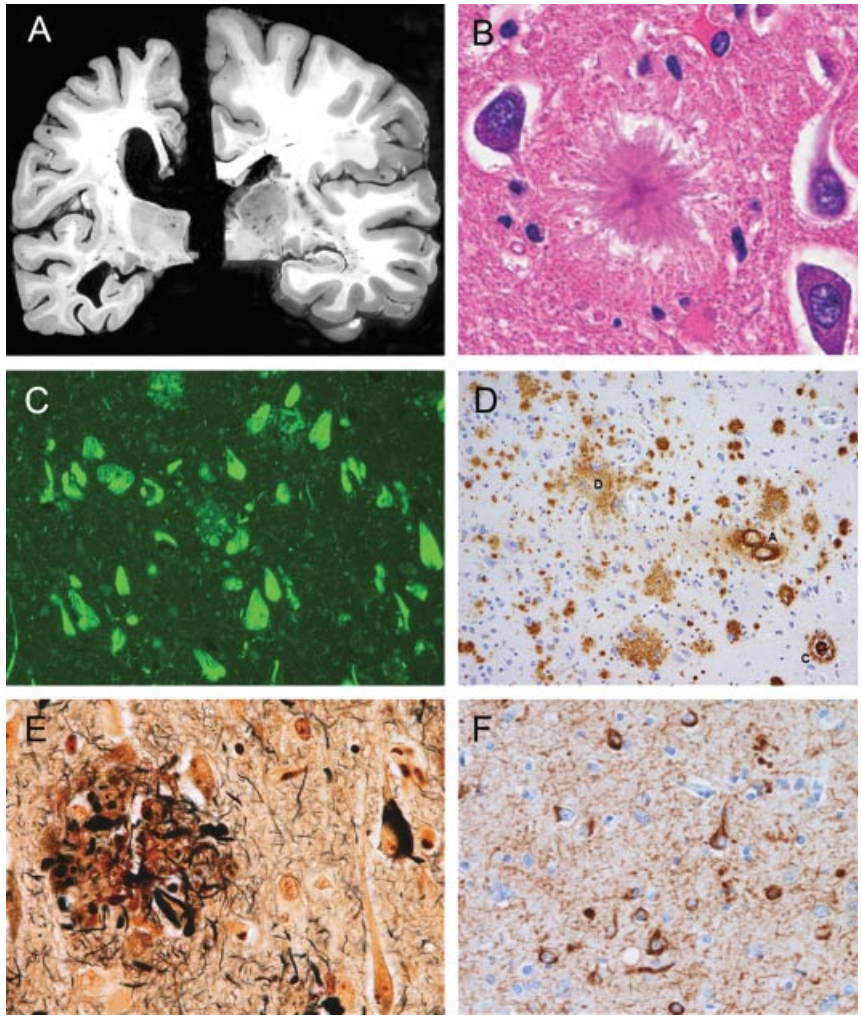


Plate 73.1 The neuropathology of AD. (a) Coronal sections of brain at the level of the hippocampus. On the left is a patient with AD, and on the right is an age-matched individual without cognitive impairment. Note the cortical atrophy and dilatation of the ventricles in the AD patient. (b) Extracellular Aβ senile plaques visualized with haematoxylin and eosin stain. (c) Thioflavin S fluorescent staining of amyloid plaques and neurofibrillary tangles. (d) Immunohistochemistry using Aβ antibodies demonstrating extracellular diffuse and fibrillar amyloid plaques and amyloid deposition in cerebral vessels. (e) Silver impregnation demonstrating fibrillar amyloid with dystrophic neurites and neurofibrillary tangles. (f) Immunohistochemistry using tau antibodies demonstrating neurofibrillary tangles and dystrophic neurites.

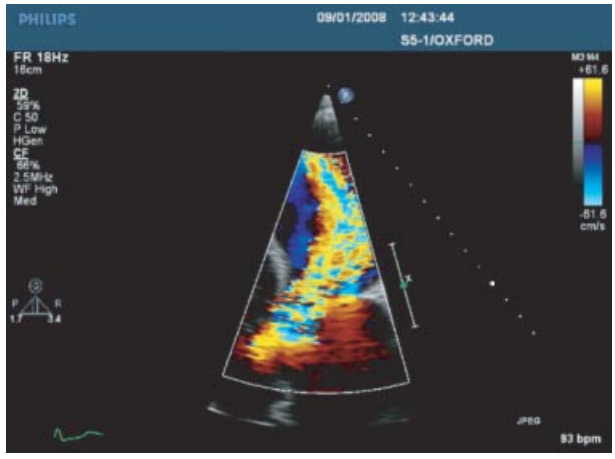
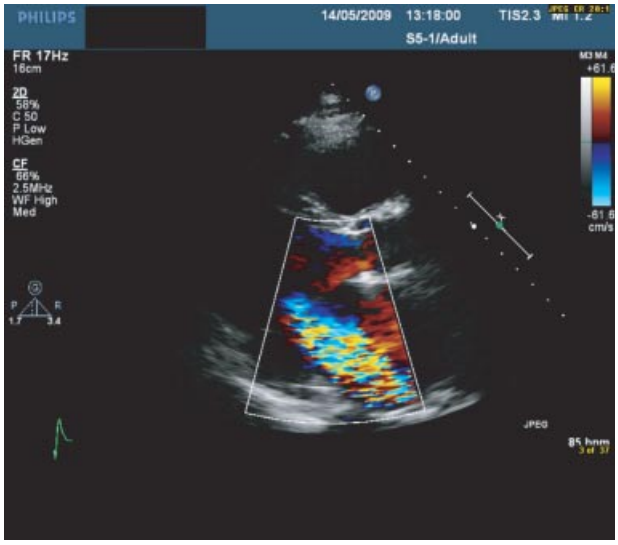
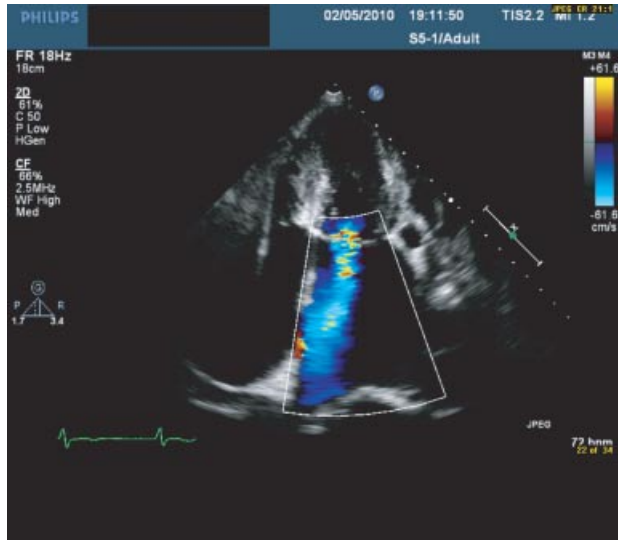


Plate 116.9 Apical five-chamber TTE view demonstrating a wide jet of severe aortic regurgitation in the left ventricular outflow tract extending to the left ventricular apex.



(a)



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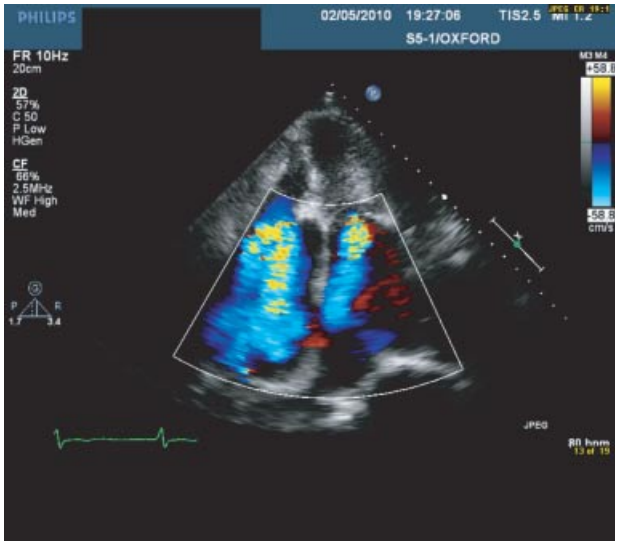

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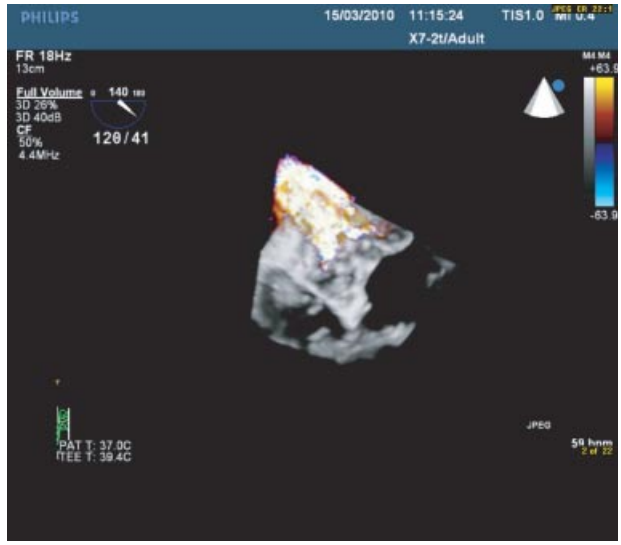


(d)

Plate 116.11 (a) TTE parasternal long-axis view with a broad colour jet across the mitral valve demonstrating severe mitral regurgitation. (b) TTE apical view demonstrating severe mitral regurgitation; the broad colour jet occupies over one-third of the left atrium. (c) TTE apical view demonstrating torrential tricuspid regurgitation and concurrent severe mitral regurgitation, causing biatrial dilatation. (d) 3D TOE demonstrating severe mitral regurgitation.

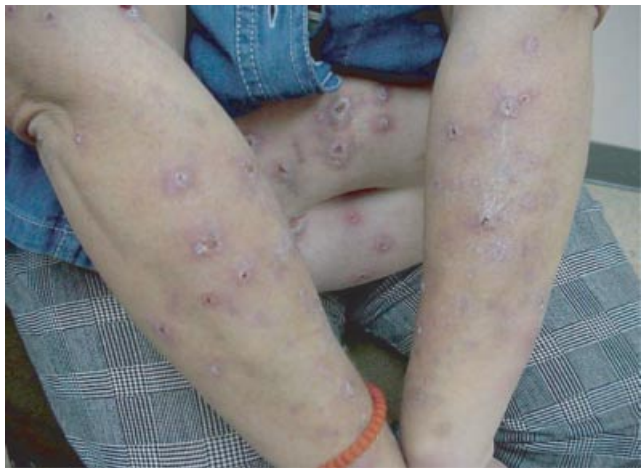


Plate 125.1 Neurotic excoriations of the arms and upper body.

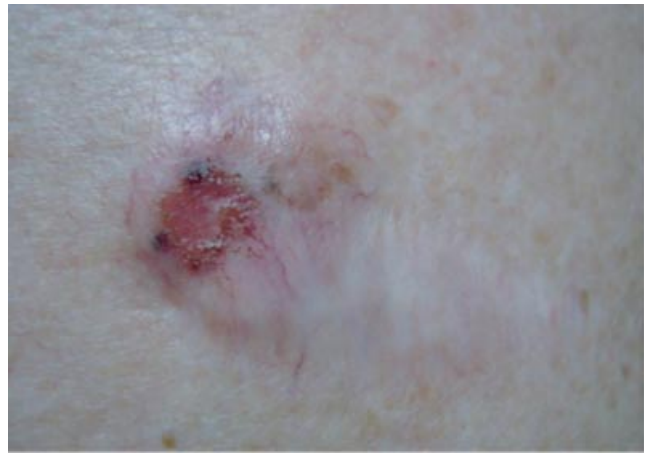
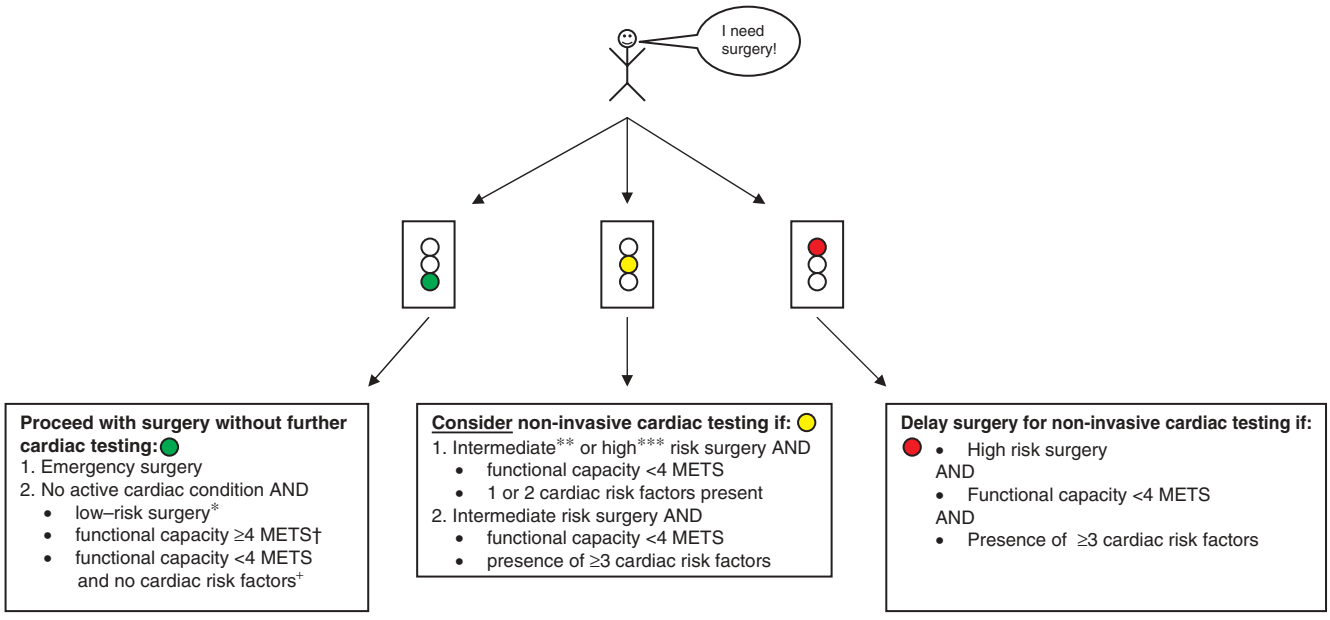


Plate 125.2 Basal cell carcinoma.



* Low risk surgery = endoscopic procedures, superficial procedures and cataract, breast and ambulatory surgeries carry <1% risk of sustaining a perioperative cardiac event

** Intermediate risk surgery = all surgeries that do not fall into low or high risk categories carry 1–5% risk of sustaining a perioperative cardiac event

*** High risk surgery = vascular surgery (aortic or other major vascular procedure and peripheral vascular surgery) carry >5% risk of sustaining a perioperative cardiac event)

† 4 METS of activity = light housework or ability to climb a flight of stairs or walk up a hill

+ Cardiac risk factors are defined by the Revised Goldman Cardiac Risk Index

Plate 127.2 Decision tree for evaluation of cardiac risk prior to surgery.

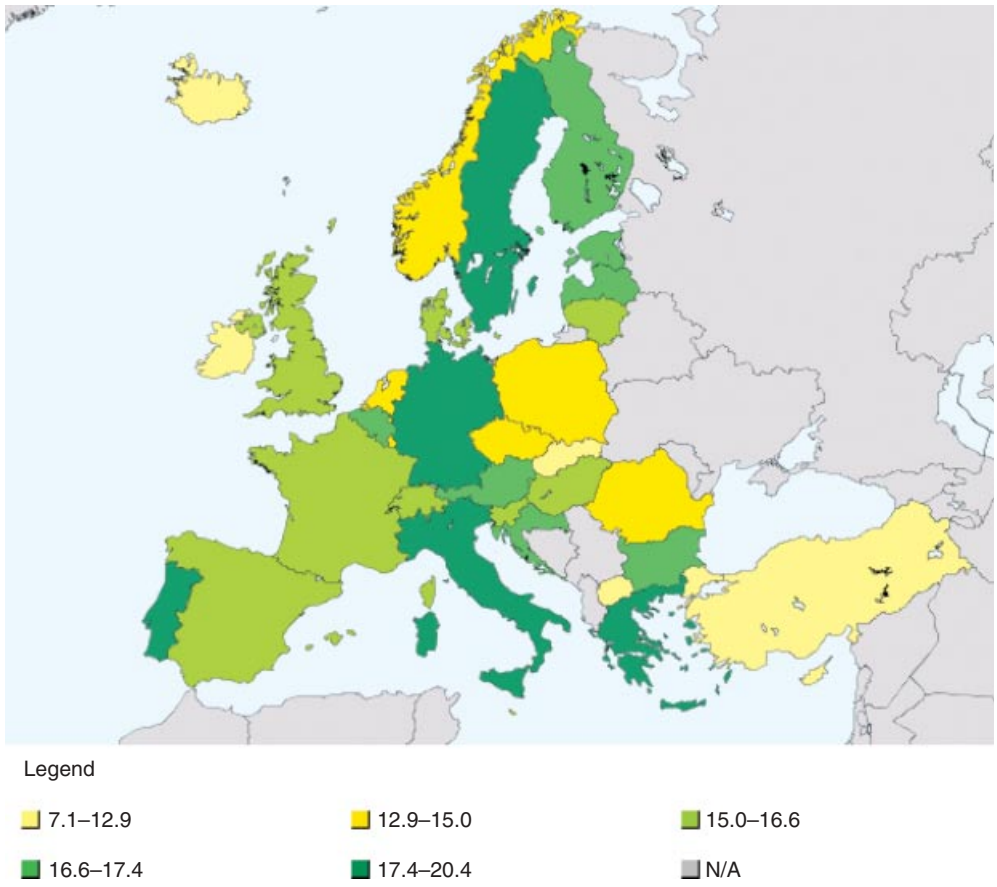


Plate 148.1 Proportion of population aged 65 and over (% of total population).

Pathy's Principles and Practice of Geriatric Medicine

FIFTH EDITION

Volume 1

Introduction: Historical perspectives

Michael J. Denham[1] and John E. Morley[2]

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Introduction

The broad subject of old age has attracted the attention of writers and philosophers for many centuries. It contains the interrelated topics of the theories of ageing, how to increase longevity, and the medical management of sick elderly people. Initially, the first two themes attracted most attention. It was not until the twentieth century that literature relating to medical care came to the fore.

The earlier writers on old age

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

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

The birth of modern geriatric medicine

Modern geriatric medicine commenced in the United States. Although American writers in the nineteenth century, such as Dr Benjamin Rush, had published on the subject of old age, the real impetus for advance came later when a young medical student, Ignatz Nascher (1863–1944), an immigrant to America from Vienna, was taken to an almshouse to see some interesting cases. An old woman hobbled up to the medical teacher with a complaint. The class was told that she was suffering from old age and that nothing could be done for her. This remark impressed him so strongly that after qualification he took up the study of the diseases of old age. His lifetime work on the subject resulted in his becoming known as the 'father of geriatric medicine'. His publication of *Geriatrics* in 1916 was followed by others, including Dr Malford Thewlis, who published the first edition of his book, *Geriatrics*, in 1919, Dr Edmund Cowdry, whose *Problems of Aging* appeared in 1939 and Dr Alfred Worcester, who published a series of lectures in 1940 called *The Care of the Aged, the Dying, and the Dead*. Dr Nathaniel Shock, in 1951, published the first edition of his classification of geriatrics and gerontology but pointed to

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

the scarcity of material. In 1942, the American Geriatrics Society was formed with a membership of physicians, and in 1945 the Gerontological Society of America was created with a multidisciplinary membership. Each of the societies produced its own journal in 1946. Unfortunately, this momentum for change was not sustained, partly because physicians saw little attraction in the subject. Interest was not reignited until the 1960s, when Medicare and Medicaid were introduced.

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

British developments

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

Hospitals did not become central to health care until the nineteenth–twentieth centuries, by which time two different types of hospitals were evolving: the voluntary hospitals and the workhouse/municipal infirmaries.[1] Voluntary hospitals, some of which dated back to the tenth century, were financed from endowments, subscriptions, fees and fund raising. They had a high reputation, with good nursing and medical staff, and acted as a base for clinical teaching of medical students. They were reluctant to admit the chronic sick, fearing that their beds could become blocked because these patients were slower in improving and there could be social problems preventing their discharge. An important consequence was that medical students rarely saw them and, therefore, were not taught about the diseases of old age or how to manage the mixture of medical and social problems they would meet after qualification.

Workhouse infirmaries were funded by local rates. They gradually became long-stay institutions for the chronic sick. Examples of unsatisfactory conditions and poor care in workhouses and infirmaries surfaced in the 1860s and resulted in visits by the *Lancet* commissioners and the inspectors of the Poor Law Board. The 1869 report of the *Lancet* Sanitary Commission was damning, stating, 'The fate of the ''infirm'' inmates of crowded workhouses is lamentable in the extreme; they lead a life which would be like that of a vegetable, were it not that it preserves the doubtful privilege of sensibility to pain and mental misery'.[2]

In 1929, the Local Government Act came into force, which aimed to correct the existing bipartite system of health care of 'one part for the pauper and the other part for the non-pauper'. However, Charles Webster concluded that health services between the two world wars were ramshackle and uncoordinated, with hostility between sections of the service, increasingly chaotic funding and with a hospital service which was unevenly distributed and limited in rural areas.[3]

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

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

An overview of early geriatric medicine in the United Kingdom

Modern geriatric medicine in the United Kingdom dates from 1926, when Dr Marjorie Warren was appointed to the West Middlesex Hospital, where her interests were initially surgical. However, in 1935 the Hospital took over control of the adjacent old Poor Law institution and Warren was put in charge of 874 patients. The situation she found was described in the first of her many articles on the modern treatment of the chronic sick.[4] At about the same time, three other British doctors were also keen to improve the medical care of the elderly: Dr Eric Brooke, Mr Lionel Cosin and Dr Trevor Howell. Like her, they, too, applied classification, diagnosis and treatment to their elderly patients, which had

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

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

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

The British Ministry of Health, which was created in 1919, and its medical officers supported the newly emerging style of medical care of the sick elderly patient with official circulars, memoranda, meetings and documents. These highlighted its firm belief in modern management of elderly patients and the drive to establish a geriatric unit in every health district. The Ministry organized surveys of hospitals in England and Wales, which were to be the basis of the forthcoming NHS. The reports, published in 1945, were generally very critical of services and accommodation for the chronic sick. 'The worst and oldest buildings were set aside for the chronic sick'.[5] 'The buildings are old, dark, devoid of modern sanitary conveniences, death traps in the case of ''fire'', and unfit for the nursing of the chronic sick'.[6] 'The first essential is that every patient should be thoroughly examined and treated with a view to restoring a maximum degree of activity'.[7] Later, Lord Amulree and Dr Edwin Sturdee, both medical officers of the Ministry, presented a paper on the care of the chronic sick to the Parliamentary Medical Committee in 1946.[8] In it they stated, 'Not only is the problem of the treatment of the chronic sick not being met, but also most people do not realize there is a problem'. In 1957, Dr Christopher Boucher, a Principal Medical Officer at the Ministry, published the result of an important survey of services available to the chronic sick and elderly.[9] However, the Ministry realized that it could not force change, but could only use persuasion to improve proper medical services for older people.[10] Perhaps this was why that, even in 1978, 42 health districts in England still lacked geriatric beds in general hospitals.

The British Medical Association played its part in planning the medical care of older people with a series of very specific reports. A coordinated geriatric service was recommended to the newly created Regional Health Authorities, supported by a wide range of domiciliary services, which would be needed by the infirm elderly to enable them to stay at home for as long as possible.[11–13]

However, commentators looked back to the old Poor Law and the new NHS with mixed feelings.[14–17] They pointed out that whereas the old Poor Law system had given a coordinated personal service to its clients, the tripartite structure of the NHS service led to lack of cooperation and coordination between the arms of the service. Chronic and mental services received a smaller share of capital and revenue, and clear guidelines for the treatment of old people were lacking. The political will to produce a nationwide effective geriatric service was lacking. On the other hand, the new service did provide the less well off with forms of care to which previously they had only limited entrée, and the elderly now had access to consultant services.

The early pioneers in geriatric medicine

In 1935, *Dr Marjorie Winsome Warren*, CBE, MB (1897–1960), was placed in charge of 874 patients from the adjacent Public Assistance Institution. These included 16 maternity patients and about 144 'mental observation' patients, who were subsequently transferred to their appropriate departments. She assessed and examined the remainder. She described the situation as follows: 'Having lost all hope of recovery, with the knowledge that independence has

gone, and with a feeling of helplessness and frustration, the patient rapidly loses morale and self-respect and develops an apathetic . . . temperament, which leads to laziness and faulty habits, with or without incontinence. Lack of interest in the surroundings, confinement to bed . . . soon produces pressure sores . . . inevitable loss of muscle tone make for a completely bedridden state . . . [leading to] disuse atrophy of the lower limbs, with postural deformities, stiffness of joints, and contractures . . . in this miserable state, dull, apathetic, helpless, and hopeless, life lingers on, sometimes for years' (Warren, 1946).[18]

She criticized the medical profession: 'It is surprising that [it] has been so long awakening to its responsibilities towards the chronic sick and aged, and that the country at large should have been content to do so little for this section of the community'.[18]

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

Mr Lionel Zelick Cosin, FRCS (1910–1993), came from a surgical background to the care of the elderly chronic sick.[19] At the outbreak of war, he was drafted to Orsett Lodge Hospital in Essex, which had been upgraded to an Emergency Medical Service Hospital in 1939. He became responsible for 300 chronic sick patients in addition to his surgical commitments. He found that they were fed and kept clean but no other treatment was given. When ordinary admissions restarted in 1944, he admitted elderly women with fractured femurs, successfully operated on them, gave them rehabilitation and discharged them home.

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

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

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

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

The second wave of geriatricians

These were led by *Lord Amulree*, KBE, MD, FRCP (1900–1983), who, prior to his appointment as geriatric physician to University College Hospital and St Pancras Hospital in London in 1949, had worked at the Ministry of Health on aspects of care of the older person. This

had brought him in touch with all the early pioneers. His appointment in geriatric medicine was, for a long time, the only one at a London teaching hospital. He and his staff classified, diagnosed and treated elderly inpatients. Assessment visits were made to old people who were on the waiting list for admission. This ensured either appropriate placement of patients in hospital or that the necessary home support was arranged to enable the person to continue to stay at home. The result was a considerable shortening of the average inpatient length of stay, increased patient/bed turnover and a reduced waiting list.

Amulree was unique amongst geriatricians in having a 'wide-angled' view of the care of elderly people. This resulted from his experience as a clinician, as a medical officer of the Ministry of Health and as a Liberal peer in the House of Lords, where he spoke on matters relevant to the care of the elderly. He wrote extensively and his work included one of the first comprehensive articles on care of the elderly.[21] He is possibly best remembered for his maxim 'Adding Life to Years', in addition to his stature, wisdom and willingness to help colleagues. He was President of the British Geriatrics Society for 25 years. When all his achievements are taken into account, there is a case for calling him 'the father of British geriatric medicine'.

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

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

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

Geriatrics in the United States

The development of modern geriatrics in strongly based on the Veterans Administration and private foundations, such as the Josiah Macy Jr Foundation, the John A. Hartford Foundation and the Donald W. Reynold Foundation. The Veterans Administration developed the Geriatric Research, Education and Clinical Center in 1976. These institutions have been the leaders in developing geriatric faculty, science and education at major universities in the United States. They also played a leadership role in developing palliative care and the teaching nursing home concept. In 1940, the Unit of Aging was started by the National Institutes of Health. In 1958, under the leadership of Nathan Shock and Reuben Andres, this became the Baltimore Longitudinal Study of Aging. The National Institute on Aging was established in 1974. Robert Butler was its first director.

There are three major geriatrics and gerontological societies in the United States. Each sponsors a yearly meeting and has its own journal. The Club for Research in Aging was founded in 1939 and it evolved into the Gerontological Society of America in 1945. The *Journal of Gerontology* was first published the following year. The Joseph T. Freeman Award was first given in 1980 to Robert Butler and its awardees read like a modern Who's Who in American Geriatrics (Table 1).

The American Geriatrics Society was formed in 1942 by Malford W. Thewlis. *The Journal of the American Geriatrics Society* was launched in 1953.

The American Medical Directors Association was founded in 1978, with William Dodd being its first president. Its journal is called the *Journal of the American Medical Directors Association*. Table 2 provides the impact factor for the major geriatric and gerontology journals.

Table 1 The Joseph T. Freeman Award of the Medical Sciences Section of The Gerontological Society of America.

Year	Recipient
1980	Robert N. Butler
1981	Isadore Rossman
1982	Manuel Rodstein
1983	R. Knight Steel
1984	Joseph T. Freeman
1985	T. Franklin Williams
1986	Charles M. Gaitz
1987	John W. Rowe
1988	Eric A. Pfeiffer
1989	Saul Kamen
1990	John C. Beck
1991	Evan Calkins
1992	Christine K. Cassel
1993	Reubin Andres
1994	Steven R. Gambert
1995	Richard W. Besdine
1996	Lissy Jarvik
1997	David H. Solomon
1998	Harvey Jay Cohen
1999	William Hazzard
2000	Mary Tinetti
2001	Robert J. Luchi
2002	Larry Z. Rubenstein
2003	Itamar Abrass
2004	John E. Morley
2005	Wilbert Aronow
2006	Molly Carnes
2007	Andrew Goldberg
2008	David Reuben
2009	Stephanie Studenski
2010	Lewis Lipsitz

Leslie Libow created the first fellowship in geriatric medicine at City Hospital Center, New York (a Mount Sinai School of Medicine affiliate) in 1966. The following year he created the first teaching nursing home in the United States. In 1982, the first Department of Geriatrics was formed at Mount Sinai Medical School. Dr Robert Butler was its first chairperson.

The first certifying examination in geriatrics was given in 1988. At the same time, 2-year geriatric fellowship programs were certified. In 1995, the fellowship requirement was lowered to 1 year. As of March 2010 there were 7029 board certified geriatrics and 1705 board certified psychiatrists in the United States. In 2008–2009 there were 470 geriatric medicine fellowship slots, of which only 62% were filled. Over two-thirds of the slots were filled by International Medical Graduates. At present there is one geriatrician for every 2699 persons aged 75 years or older in the United States. At the present rate of recruitment into geriatrics, this will decrease to one for every 5549 older Americans by 2030. Physicians working in nursing homes can be certified separately by becoming a Certified Medical Director, which is offered by the American Medical Directors Association.

Over the last 30 years, the United States has taken the lead in developing the scientific base of modern geriatrics. Unfortunately, the lack of interest by young physicians in geriatrics is likely to erode this over the next decade.

Geriatrics in the rest of the world

The first geriatrics society in France was formed in 1939 under the leadership of A. Baudouin. In the modern era, Professor Bruno Vellas, whose father developed the University of the Third Age, has revolutionized the approach to geriatrics in France. He founded the *Journal of Nutrition Health Aging* as the premier ageing journal in Europe. He developed the Mini Nutritional Assessment. His centre at the University of Toulouse has become a leader in modern research in nutrition, Alzheimer's disease and nursing homes.

In Italy, 'Recover' (old people's homes) was established by the Catholic Church in the mediaeval period. At the start of the twentieth century, hospital departments for the care of older persons and the disabled were formed. By the middle of the twentieth century, there were long stay hospital units ('lungodegenza'), rehabilitation units ('infermeria') and rest homes ('casa di riposo'). The Geriatric Society in Italy was formed in 1949. M. Ascoli was the first chair. Italy has two longitudinal studies on ageing, namely the Italian Longitudinal Study on Aging (ILSA) and the InCHIANTI (Invecchiare in Chianti).

In Sweden, the first chairs of geriatrics were established in Uppsala University and Göteborg (Gothenburg) University. Under the leadership of Alvar Svanborg and Bertel Steen, the longitudinal population study of persons over 70 years of age was established in Gothenburg in 1970–1971. The work of Torben Gill at the Old People's Town in Copenhagen from 1936 led to Denmark establishing a specialty of long-term care. In 1972, the Danish Society of Geriatric Medicine was founded.

The Spanish Society of Geriatry and Gerontology was started in 1948. A. Baudouin was the first chairperson. Geriatrics has been a recognized medical specialty since 1978, with a 4-year training program. Switzerland played a major role in the development of geriatric psychiatry under the leadership of Professor J.-.P Junod, who became the first Professor of Geriatrics in 1962. The University of Geneva has developed a Department of Geriatrics. Jean-Pierre Michel developed the European Academy for Medicine of Ageing (EAMA) in Sion, a centre for training young geriatric faculty.

The leader in geriatrics in Japan is the Tokyo Metropolitan Institute of Gerontology, which was founded in 1972. It is

Table 2 Citation data for journals in geriatrics and gerontology for the year 2009.

Rank	Abbreviated journal title	Impact factor	5-year impact factor	No. of articles in 2009
1	*Aging Cell*	7.554	7.207	70
2	*Neurobiol Aging*	5.937	6.239	205
3	*Age*	5.839	4.595	33
4	*Ageing Res Rev*	5.622	6.328	32
5	*Mech Ageing Dev*	4.179	3.914	93
6	*Rejuv Res*	4.138	3.383	40
7	*J Am Med Dir Assoc*	3.709		88
8	*J Am Geriatric Soc*	3.656	4.460	299
9	*Am J Geriatr Psychiatry*	3.353	3.842	100
10	*Exp Gerontol*	3.342	3.404	107
11	*Age Ageing*	3.131	3.454	129
12	*J Gerontol A Biol*	3.083	3.815	165
13	*Biogerontology*	2.816	2.803	55
14	*Dement Geriatr Cogn*	2.578	2.887	151
15	*Int Psychogeriatr*	2.506	2.629	132
16	*Drug Aging*	2.209	2.340	82
17	*J Gerontolol B Psychol*	2.094	2.825	100
18	*Maturitas*	2.093	2.079	173
19	*Int J Geriatr Psychiatry*	1.981	2.425	178
20	*J Geriatr Psychiatry Neurol*	1.915	2.581	31

associated with a 700-bed geriatric hospital. The National Institute of Longevity Science was established in 1995.

The first International Congress of Gerontology was held in Liège, Belgium, in 1950. In 1952, the second congress held in St Louis led to the formation of the International Association of Gerontology. This has recently been renamed the International Association of Gerontology and Geriatrics (IAGG). In conjunction with the World Health Organization (WHO) and under the leadership of Professor Vellas, the society has become more active. As a result, they have recently published guidelines developed by a task force chaired by John Morley and Yves Rolland, to enhance care in nursing homes (Table 3).

Teaching geriatric medicine

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

However, research on attitudes of medical students toward the elderly has shown that they tend to lose their initial interest and empathy for older people as they train and qualify. A survey of their attitudes before qualification showed that they had empathy for, and a 'bedside interest in', the elderly, which disappeared after graduation when the doctors considered their career prospects.[22] Parkhouse and McLaughlin[23] found that no doctor who had graduated in 1974 wished to enter geriatric medicine. Lambert *et al*.[24] showed that little had changed in a review of career preferences among newly qualified doctors: preferences for geriatric medicine remained very low at 0.9%, well below general medicine and surgery, although above genetics. Factors blamed included the prejudice of medical teachers against geriatric medicine, poor image/role of the geriatrician and mediocre working conditions. As a result, recruitment of medical staff into the specialty was poor. The Royal College of Physicians responded in 1972 and 1977 with a range of recommendations, including integration of geriatric medicine with general medicine, appointment of consultant physicians with a special interest in geriatric medicine and rotation of junior training posts between the two specialties.[25,26] The College also introduced the

Table 3 The IAGG Task Force recommends the following.

No.	Recommendation
Recommendation 1	Effective leadership structures are established, that where possible, include an expert physician (medical director), and an expert registered nurse (nursing director) and skilled administrator
Recommendation 2	An international alliance is formed to develop nursing home leadership capacity and capabilities
Recommendation 3	To showcase international exemplars of excellence in nursing home practice to raise awareness of the demonstrable benefits for older people and high standards achieved through expert practice
Recommendation 4	To create positive working conditions for nursing home practitioners with attractive career development opportunities, recognition and similar rewards enjoyed by health care workers in comparable roles within the acute care services
Recommendation 5	That nursing home quality indicators are developed that are sensitive to clinical and care needs and the right of older people to care that is dignified and respectful
Recommendation 6	The use of physical and chemical restraints should be reduced to those that are absolutely indispensable
Recommendations 7	That 'meaningful activities' be offered to residents to provide physical and mental exercise and opportunities to participate within the nursing home and in community life, enhancing personal autonomy, social relationships (including intergenerational relationships), and social support
Recommendation 8	That evidence-informed pain assessment and management programmes are introduced into all nursing homes
Recommendation 9	That evidence-informed end of life and palliative care programmes are introduced into all nursing homes
Recommendation 10	National drug approval agencies consider requiring drug trials that are age appropriate and inclusive of nursing home residents before they are approved
Recommendation 11	IAGG develop international certification courses for nursing (care) home health professionals
Recommendation 12	Pilot the use of 'Community of Practice Models' as a practice improvement method for nursing homes, utilizing both face-to-face interdisciplinary training and virtual team support
Recommendation 13	A universal ethical approach to obtaining informed consent and monitoring the appropriateness of research is developed
Recommendation 14	Develop nursing home research capacity in developing nations
Recommendation 15	An investment is made in research priorities that address major public health problems and inequalities that affect older people receiving long-term care. Research priorities for which a high need is recognized include: a A worldwide survey of different models of care, nursing home structure and issues in improving quality of care is undertaken b A worldwide survey of older persons and their families is undertaken to determine their preferences for long-term care c A cross-national, prospective epidemiological study measuring function and quality of life in nursing homes d Development of culturally appropriate standardized assessment instruments including those involving social participatory methods e A function-focused approach of the prevalence of geriatric syndromes, their impact on function and development of strategies to improve care for these syndromes needs to be developed f Research that evaluates the impact of different models of care against trajectories of physical and cognitive function

Diploma of Geriatric Medicine in 1986 to encourage general practitioners to gain interest in the care of older people.

Achievements of geriatric medicine

Gerontology: the science of the ageing process

Interest in gerontology in the United Kingdom was stimulated by the support of charitable foundations and the enthusiasm of a few individuals. The Nuffield Foundation created a medical and biological Research Committee, which gave grants to Howell for his research, to Dr Alex Comfort to work with Sir Peter Medawar at Birmingham, and later at University College London, and to Professor Sir Frederick Bartlett at the University of Cambridge to establish a research unit to investigate the psychological aspects of ageing. The Nuffield and the Ciba Foundations supported Vladimir Korenchevsky (1880–1959), a Russian biologist, who had studied under Pavlov and Metchnikoff. His enthusiasm for the science of ageing culminated in his becoming director of the Oxford Gerontological Institute. He was a driving force behind the creation of the International Association of Gerontology (IAG). The Ciba Foundation supported the IAG, which held its first meeting in 1950 in Liège, Belgium. The first meeting of the clinical

section of the IAG was held in Sunderland in the United Kingdom in 1958 and was chaired by Dr Oscar Olbrich. A later meeting was held in Manchester in 1974, which was organized by Professor Brocklehurst. The Ciba Foundation maintained its interest in old age by establishing a series of special colloquia in London, which were attended by many international experts on ageing, and supported the British Society for the Research in Ageing, which was founded by Korenchevsky.

As the new-style treatment methods were applied to the previously neglected chronic sick, clear evidence emerged of its effectiveness, particularly in hospitals. Official health data sources, such as Hospital In Patient Enquiry (HIPE) data collection, the Office of Health Economics and Health and Personal Social Services Statistics for England, showed that the number of deaths and discharges of elderly people and patient turnover from geriatric wards steadily increased while the average and median lengths of stay decreased. In 1980, the Chief Medical Officer for England and Wales was able to report 'the average length of stay for patients in hospital departments of geriatric medicine is steadily diminishing – more so than in any other hospital specialty. Only 10% remain in hospital for more than 6 months; the median length of stay is only 21.7 days'.[27] Progress was such that in 1984, the Nuffield Provincial Hospital Trust was able to comment, 'It [geriatric medicine] has established its expertise and has had notable success in developing and raising the standards of services for the old'.[28] Concomitant with these developments, individual geriatricians began to create differing styles of practice: whereas some did not take emergency admissions, others took increasing numbers of acutely ill patients, and still others reintegrated with general medicine, taking part in unselected acute medical intake and joint ward rounds with their general physician colleagues.

Problem areas

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

Another concern was the quality of care given to the elderly in hospital. This culminated in the publication in 1967 of *Sans Everything: a Case to Answer*, which alleged inappropriate care in hospitals for the elderly and mentally ill. Official investigations found that the complaints were inaccurate, vague, lacking in substance, misinterpretations or over-emotional.[29] Following yet another allegation of improper care in a unit for the mentally subnormal in 1967, the Secretary of State for Health created the Hospital Advisory Service (HAS) in 1969, which was to act as his 'eyes and ears'. It was to be responsible only to him and was to be independent of the Department of Health. Visits to hospitals for the elderly and mentally ill started in 1970 and were carried out by teams of 'in-post' professionals: consultant geriatricians or psychiatrists, senior nurses, paramedical staff, administrators, and later social workers. It is best considered as a form of 'peer review'. Later its remit was extended to cover community services, at which time it was renamed the Health Advisory Service.

The development of specialist service for the elderly mentally ill lagged behind that of the physically ill. Not infrequently, these patients were inappropriately admitted to geriatric wards, where staff had limited experience in managing them. Sometimes they were admitted to large general mental hospitals where the general psychiatrists did not welcome them. The Ministry was aware of the problems presented by these patients and published advisory documents.[30,31] Eventually, guidelines were introduced to ensure admission to an appropriate ward: assessment by a multidisciplinary team was recommended. Joint assessment units with input from the local authority, psychiatrists, and the geriatrician were set up, although they tended to silt up owing to the failure to move the patients on to suitable wards or accommodation. Psychogeriatric day hospitals were opened, which provided a useful community function. Local authority residential homes were encouraged to take more mentally ill patients. However, it was not until the 1970s that consultant psychogeriatricians were appointed.

Another source of debate was the term *geriatrics* and allied words. The word *gerocomy*, attributed to Galen, was used for the medical care of the elderly and was adapted to *geroncology* for their sociological aspects. In 1903, Metchnikoff invented the word *gerontology* for the biological study of the ageing process. Nascher is generally credited with coining the word *geriatrics*.[32] 'The term was . . . derived from the Greek, *geron*, old man and *iatrikos*, medical treatment. The etymological construction is faulty but euphony and mnemonic expediency were considered of more importance than correct grammatical construction'. Howell pointed out

at least one author who had confused *gerontology* (the science of old age) and *geriatrics* (the care of the aged). The word *gerontology* has been attacked as a barbarous misspelling and the word *geratology*, the study of old age, has been suggested instead. The founders of the Medical Society for the Care of the Elderly did not use the word *geriatrics* since it was, in 1940s, almost unknown. Many United Kingdom hospital geriatric units, aware of the public's perception of *geriatrics* as being apparently synonymous with *senility*, now call themselves 'Department for the Medical Care of the Elderly' or 'Care of the Elderly Department'.

Key points

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

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PART 1

Ageing: Biological, Social and Community Perspectives

CHAPTER 1

A biological perspective of ageing

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Introduction

This chapter provides an introduction to the 'principles and practice of geriatric medicine', the topic of this textbook. Underlying the need for geriatric medicine are the biological changes with time that we call ageing. The purpose of this chapter is to summarize what we know about these changes, how they relate to the diseases and conditions that require medical intervention and why they even occur at all.

This chapter develops several themes. Biological ageing progresses differently in different cells, tissues and organisms. Age theories focusing on one concept are common, for example, free radical, genetic, neuroendocrine, and immune, but they are incomplete in themselves. And finally, there are multiple gaps in our knowledge concerning the causes of ageing.

Ageing populations

In talking about biological ageing, it is useful to talk about the ageing of whole populations. Although the age at death of an individual varies widely, the survival of whole populations is fairly predictable, and the curves have a similar shape across species. Figure 1.1 shows human survival curves for people in the United States. Each curve represents survival data (percentage surviving) at each age for the calendar years indicated. The survival curves are sigmoidal, and they are characterized by very few deaths in the early years, a short period with a large number of deaths and a tail of old survivors. The age at which the number of survivors starts to decrease rapidly is usually referred to as the onset of senescence. The slope of the curve during the decrease is the rate of senescence, and the age where there are no survivors is the maximal lifespan.

In 1900–1902, there was an early drop in survival, due to infant mortality, followed by a somewhat gradual decline, and ending with a steeper decline between age 70 and 90 years. As the calendar years progress from 1900–1902 to 1949–1951 to 2006, there were many more survivors at each age and a delay in the onset of senescence. This is sometimes referred to as the squaring off of the survival curve. Much of the difference between 1949–1951 and 2006 was due to a delay in the onset of senescence with little change in the rate of senescence (the slope of the decline). Also, the maximum lifespan was similar for all curves. The net effect is that the average lifespan has increased largely through a delay in the onset of senescence with little change in the rate of senescence or in maximal lifespan.

The dotted line represents a theoretical population where the onset of senescence has been further delayed but with an increase in maximal lifespan. This is the type of shift that is seen with caloric restriction of animal models.[1] To see such a change in human populations would most likely require a fundamental change in our biological ageing. It would not arise from more effective treatment of the diseases of ageing, which would tend to square off the existing survival curve.[2,3]

Although survival curves are useful, they show only one rather dramatic endpoint – death. As more people live longer, there is greater interest in quality of life rather than just the length of life. This has given rise to the concept of 'functional lifespan', which can be assessed by various clinical measures. One challenge in the biology of ageing is to develop markers that reflect physiological age rather than just chronological age. Such markers could be used for early intervention with the goal of extending functional lifespan.

Why do we grow old?

The question of why we grow old can be answered at many levels – philosophical, religious and biological – and, of course, becomes more relevant personally the older we become. Recent research and thinking form a framework in which to wrestle with the question of why we grow old biologically. This question was proposed as an 'unsolved problem of biology' by Medawar in 1952.[4] However, recent concepts have led two prominent gerontologists to

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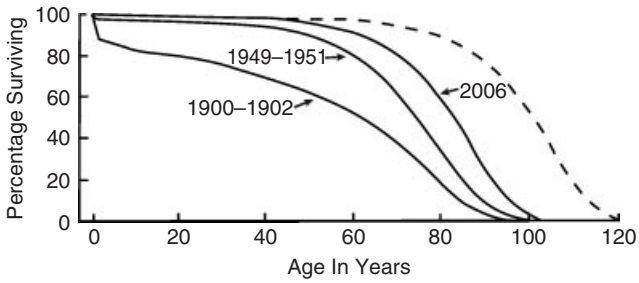

Figure 1.1 Human survival curves. Percentage surviving versus age is plotted for each of the calendar years indicated. Data redrawn from the National Center for Health Statistics (US Bureau of the Census). The dashed line represents a theoretical shift in the data for 2006. The data are shifted such that the age of onset of senescence and maximal lifespan are increased, but there is no change in the rate of senescence.

conclude that 'aging is no longer an unsolved problem in biology'.[2,5] The reason for this change is that since Medawar first posed the question there has been a large amount of descriptive gerontology – a cataloguing of the physiological and biochemical changes that characterize ageing in many different organisms. As a result, within about the last 20 years biologists have begun to look at the big picture of why we age.

The question of why we grow old is really tied into a fundamental characteristic of life itself – reproduction. Simply put, if the purpose of a particular species is to maintain itself through reproduction, there is no reason to invest biological resources in maintaining a member of that species after the birth and nurturing of the next generation. Hence, after reproduction, species generally decline physiologically and eventually die. This broad perspective is usually referred to as 'the evolutionary theory of ageing', and it makes important predictions about the biology of ageing.

The evolutionary perspective of ageing – key concepts

The evolutionary perspective of ageing is made up of three interrelated concepts[3,5] – mutation accumulation, antagonistic pleotrophy and disposable soma (Table 1.1).

Mutation accumulation

The 'mutation accumulation' concept was postulated by Medawar in an attempt to answer his own question about why we age.[4] It states that genes may accumulate that are expressed only after reproduction. These genes may have deleterious effects that contribute to the physiological decline of the organism. These late-acting genes are not selected against because they do not affect reproduction and nurture of the next generation.

Table 1.1 Evolutionary perspective of ageing.

Mutation accumulation	Genes may accumulate that act late in life and contribute to the physiological decline of an organism
Antagonistic pleotrophy	Some genes may have positive effects early in life but then have negative effects later in life after reproduction
Disposable soma	There is a competition for resources between reproductive (germ line) cells and maintenance (somatic) cells, and after reproduction the somatic cells are no longer needed (disposable)

Antagonistic pleotrophy

An extension of the mutation accumulation concept is the idea that these late-acting genes may exist in the gene pool because they have positive effects early in life. Thus, the same gene may have positive effects early in life but negative effects after reproduction. This concept is called 'antagonistic pleotrophy'. An example would be the fact that a particular apolipoprotein (ApoE4), which is a significant risk factor for Alzheimer's disease, maintains itself in the population. Since Alzheimer's disease arises very late in life after reproduction, there is no selective pressure to remove it from the gene pool. The fact that ApoE4 is still found in the gene pool may mean that it gives some positive advantage early in life.

Disposable soma

For a species to survive, it must reach reproductive age and nurture the next generation. Since organisms have only a limited amount of biological resources at their disposal, these resources must be allocated carefully between maintenance and reproduction. This is sometimes looked at as a competition between the cells involved in maintenance (the somatic cells) and the cells involved in reproduction (the germ line cells). In such a competition, the most important thing is for the germ line cells to be passed on to the next generation. The somatic cells (the vast majority of the cells in the body) are only a means to that end. In that sense, somatic cells are 'disposable' after they have supported the organism through reproduction. Hence this concept has been named the 'disposable soma' theory. There is no incentive to maintain the stromal cells past the reproductive age, and a long post-reproductive lifespan could be viewed as wasteful.

Changing concepts in the biology of ageing

The descriptive work and the evolutionary perspective have changed the way in which we look at a number of

Table 1.2 Changing concepts in the biology of ageing.

Older concepts	Newer concepts
There is a genetic programme that controls the ageing process much like there is a developmental programme	Ageing is not the result of a 'programme' but rather the result of 'biological neglect' after reproduction
Biological ageing is a singular process that affects all tissues and organisms equally	Biological ageing has many components that affect tissues and organisms in diverse ways
There is one 'theory of ageing' that explains the ageing process in biological terms	Biological ageing is complex change with time that is described by multiple perspectives (theories) at multiple levels
Ageing is due either to our environment (extrinsic) or to our genes (intrinsic)	Ageing is roughly 25–35% genetic with the rest influenced by our environment and lifestyle
Maximal lifespan is characteristic of an organism and is fixed	Maximal lifespan can vary within limits in response to the nutritional and reproductive needs of the organism
Ageing is the sum of all of the diseases of ageing	Ageing results in an increase in disease, but it is separate from the diseases of old age

important concepts in the biology of ageing. In a sense, the fields of geriatrics and gerontology have been around long enough so that there has been an 'ageing' of the concepts related to biological ageing (Table 1.2)

There is no 'genetic programme' for ageing

Previously, ageing was viewed as a 'process' or even a 'programme'. Much like a developmental programme, it had its own intrinsic clock that moved inexorably towards universal senescence and death. At various times, this clock has been postulated to be hormonal (hypothalamus–pituitary axis), immune (involution of the thymus) or cellular (cell senescence). However, from an evolutionary perspective, ageing is not a genetic program but rather the result of biological neglect (not necessarily benign) that occurs after reproduction is complete.

Biological ageing varies with tissue and organism

Since there is no programme, there is no reason to expect that biological ageing will progress the same in all organs of an individual or in all species. The death certificate of a mouse may look very different from that of a human. For example, laboratory rodents often die of kidney disease, but this is a much lesser cause of mortality in humans.

There is no one 'theory of ageing'

Another result of this lack of post-reproductive maintenance is that different organ systems will fail at different rates across tissues and organisms. That is, biological ageing is probably not due to a single universal deficit in all organisms. Put another way, there is no one mechanism or 'theory of ageing' that explains everything. However, the classical theories of ageing describe important aspects of biological ageing (see below).

Ageing has both genetic and environmental components

Some researchers have made a sharp distinction between ageing due to environmental factors and ageing due to genetic factors.[2] They classified theories of ageing as either extrinsic (environmental) or intrinsic (genetic). It is becoming clearer that ageing is influenced by both environment and genetic makeup, and it is sometimes difficult to untangle the two. There definitely is a genetic component, as the best predictor of lifespan is the lifespan of one's parents. Studies of twins suggest that in humans about 25–35% of ageing is genetic and the rest is environmental. Recently, studies of centenarians have found certain genes that seem to be associated with long life. These are sometimes referred to as 'longevity assurance genes'. The idea is that these genes contribute to long life, but they are not part of a genetic mechanism to regulate lifespan.

Maximal lifespan can vary within limits

The lifespan of a group of genetically related animals (inbred laboratory rodents under laboratory conditions) is remarkably constant, even though it is not directly regulated. This has led to the concept that lifespan, especially in higher organisms, is fixed. Yet the lifespan of lower organisms (worms, flies, yeast) can be markedly altered by a variety of manipulations. These include restricting diet, boosting antioxidant defences and modulating insulin/growth signalling pathways (see below). However, modulating the lifespan of higher organisms such as mammals seemed difficult, except through caloric restriction.[1] Recent studies have suggested that higher organisms have 'longevity assurance pathways' that parallel those in lower organisms.[6] Modifying these pathways in various ways has made it possible to extend life in mice. Thus, even higher organisms have the ability to modulate their lifespan based on reproductive needs and environmental conditions.

Ageing is not the sum of the diseases of ageing

The relationships between ageing and the diseases that accompany ageing are still the subject of some debate.[3] Previously there was a tendency to identify ageing with the diseases of ageing. More recently, the emphasis has been that these diseases may be due to underlying biological changes with age. In other words, increased vulnerability to disease is a characteristic of biological ageing, but ageing is not just the sum of all of the diseases of ageing. The distinction between ageing and the diseases of ageing is very important in terms of research strategies. If ageing is mostly the diseases of ageing, then these diseases will have to be slowly conquered one by one. On the other hand, if there are underlying biological processes driving disease, then understanding and modifying these could possibly reduce the vulnerability to many diseases at once.

The 'theories of ageing'

Although there is no universal 'programme' of ageing, when one looks across species there are common themes as to how organisms age. These have led scientists to propose various 'theories of ageing' over the years based on experimental observations. These theories used to be viewed as rivals, but they are really complementary. They each describe some aspect of biological ageing at some level of organization. Since none of these theories gives a complete picture, it may be more useful to refer to these 'theories of ageing' as 'components' or 'perspectives' of biological ageing.

Over the years, there have been many 'theories of ageing' proposed and many attempts to organize them. In a review paper in 1990, Medvedev identified over 300 theories of ageing.[7] There have been a number of more recent reviews describing the theories of ageing in an organized way.[8–10] In this chapter, we describe some of the major theories that have been helpful in characterizing aspects of the biology of ageing.

One way to organize the theories is according to the level of biological organization that they address.[8,10] Complex biological organisms are composed of multiple organ systems, made up of individual organs, made up of individual cells, made up of subcellular organelles and individual molecules. So we can talk about the subcellular, cellular, and systemic components of ageing (Table 1.3) These components seek to describe *how* we age (increased damage, decreased repair, etc.) whereas the evolutionary concepts (Table 1.1) seek to describe *why* we age.

Subcellular components of ageing

The free radical perspective

One of the most important concepts in the biology of ageing over the last 50 years is the free radical perspective of

Table 1.3 Components of biological ageing.

Components	Type	Description	Ref.
Subcellular components	Free radicals	Free radicals generated by cells produce oxidative damage to proteins, DNA and lipids, impairing cell function	13, 14, 16
	Mitochondria	Energy production by mitochondria generates free radicals that cause local oxidative damage and further degrade mitochondrial function	17, 18
	Gene expression	DNA damage results in altered gene expression and accumulation of non-functional proteins, altering cell function	19–21
Cellular components	Cell senescence	Somatic cells stop dividing due to a programmed limit or due to cellular stress and damage, affecting the surrounding tissue	24, 25
	Stem cells	The capacity of resident stem cells to divide and replace damaged tissue declines with age	26–28
Systemic components	Neuroendocrine system	Multiple changes in hormone secretion, action and feedback result in altered responsiveness to internal and external stressors	31–33, 36
	Immune system	Changes in the number and function of immune cells result in decreased capacity to counter new challenges and respond to vaccines	38, 39

ageing. The importance of free radicals was first proposed by Harmon in 1956.[11] Free radicals are highly reactive chemical species that are formed as a byproduct of certain biochemical reactions. A major source of free radicals is the production of energy by oxidative phosphorylation in the inner mitochondrial membrane. Certain other biochemical processes also produce free radicals, in addition to ionizing radiation and environmental pollutants. These reactive chemical compounds then produce oxidative damage to important cellular molecules such as proteins, DNA and lipids. Such damage can then affect homeostasis at the cellular level, resulting in cell senescence, and/or uncontrolled cell growth (see below). Because the free radical reactions produce oxidative damage, the free radical theory is sometimes referred to as the 'oxidative stress' theory.[12]

One of the important contributions of the free radical perspective is that it makes several experimental predictions, many of which have been borne out. First, in experimental animals, oxidative damage to proteins, DNA and lipids has been shown to increase with age.[13] Second, species that are longer lived are less susceptible to oxidative stress,[14] and they have more efficient repair mechanisms. More free radicals are generated by a high metabolic rate, and a high metabolic rate is associated with a shorter lifespan. Third, caloric restriction of organisms increases their maximal lifespan and tends to increase their antioxidant defences and reduce oxidative damage.[1] Finally, organisms which have their antioxidant defences boosted artificially live longer. This has been demonstrated in fruit flies, roundworms and mice.[15]

An important byproduct of free radical production is an acceleration in the non-enzymatic coupling of glucose with proteins – glycosylation. A common example of this is the high levels of glycosylated haemoglobin in the blood of diabetics. Glycosylation increases with age and may interfere with protein function. Glycation may play a role in the ageing of connective tissue, blood vessels and the lens of the eye.

More recently, the importance of free radicals and oxidative stress in determining maximal lifespan have been called into question. One reason is that a systematic knockout of components of the antioxidant systems in mice has failed to shorten lifespan.[16] However, there may be enough redundancy built into the antioxidant systems that more than one system must be knocked out to see an effect. Second, numerous attempts to extend lifespan through dietary antioxidants have been negative. However, human studies have shown that diets high in antioxidants correlate with positive outcomes. Thus, antioxidants may be used more efficiently in the body when consumed as part of a diet. In addition, although it may be difficult to show an effect of free radical manipulation on lifespan, free radicals may play an important role in some of the morbidities of ageing such as cancer and cataract formation.

The mitochondrial perspective

Since most of the free radicals in cells are generated by mitochondria, it is only a small jump from the free radical perspective to the mitochondrial perspective of ageing. Since free radicals do not travel very far before reacting, this component has focused on local damage to mitochondrial proteins, DNA and lipids. Again, there is experimental evidence to support this concept. It has been shown that oxidative damage to mitochondrial proteins and DNA increases with age.[17] Mitochondrial DNA codes for some of the proteins that are important for mitochondrial energy production. Oxidative damage to mitochondrial proteins and DNA may then lead to inefficient energy production and the release of more free radicals. This downward spiral may account for the fact that mitochondria in older aerobic tissue such as skeletal muscle are fewer in number, have an altered appearance, and are less efficient in energy production. On the other hand, altered expression of mitochondrial antioxidant enzymes does not show a clear effect on lifespan in mice.[18]

The gene expression perspective

A third major subcellular component of ageing is the gene expression perspective. In its broadest sense it relates to changes in information flow between DNA, mRNA and proteins. DNA is subject to strand breaks, covalent modifications and chromosomal rearrangements. This may result in altered gene expression and contribute to the ageing process.[19,20] Much DNA damage is in the form of chromosomal rearrangements. Such rearrangements are usually associated with diseases such as cancer rather than with biological ageing as a whole. With the advent of inexpensive gene arrays, there have been many reports of changes in gene expression in various tissues and in various models of ageing. However, it difficult to know whether the observed changes reflect primary changes that are part of general biological ageing. In many cases, the changes could be in response to age-related disease or to a general increase in oxidative stress.

Since DNA damage ultimately leads to changes in proteins, it has been proposed that the number of abnormal proteins may increase with age. This has been referred to as the 'error catastrophe' theory. Although an increase in abnormal proteins can be detected in some circumstances, there does not appear to be a general increase in dysfunctional proteins. Interestingly, it may be that changes in the turnover of certain proteins with age is important. Protein turnover may play an important role in the development of certain neurological diseases characterized by abnormal protein aggregation.[21]

Cellular components of ageing

The cell senescence perspective

For the number of cells in a tissue to remain constant, there must be tight control over the rate of cell production and cell death. Uncontrolled production by cell division can lead to cancer and uncontrolled cell death can lead to tissue dysfunction and disease. Cell death can take the form of senescence (cells stop dividing), apoptosis (purposeful cell death) or necrosis (cell death usually due to insults). Cell senescence seems to have the most relevance with regard to ageing of the whole organism.

The phenomenon of cell senescence was originally described by Hayflick and Moorehead, who found that human skin fibroblasts divide only a finite number of times (population doublings) even under optimal growth conditions.[22] Initially, the number of population doublings seemed to correlate with donor age (inversely), with the longevity of donor species (directly) and with certain human premature ageing syndromes (decreased). Because of this possible correlation between population doublings and ageing of the whole organism, there was an intense effort to determine what regulated the number of cell divisions at the cellular level. It was finally established that a major determinant of population doublings was the length of telomeres, structures that play a protective role on the tips of chromosomes. Cells that divide indefinitely (germ cells, cancer cells, stem cells) contain an enzyme called telomerase that repairs the telomere shortening after each cell division.[23]

Recently, it has become clear that telomeres and telomerase are not the sole factors regulating cell senescence. Cells can undergo stress-induced senescence in addition to replicative senescence.[24] Cell senescence can also be induced by free radical damage and DNA damage that acts via independent cellular pathways.[25] Thus, cell senescence may be a consequence of the free radical and DNA damage components of ageing described previously. Also, telomere shortening has been difficult to observe in rodents, which nevertheless age in ways analogous to humans. However, telomere length and cell senescence may contribute to the ageing of certain tissues. In particular, it may contribute to the ageing of stem cells (see below). In the big picture, then, cell senescence may function more to prevent uncontrolled cell growth (cancer) rather than as a 'clock' to limit lifespan. Also, some of the original correlations between cell senescence and organismal ageing have been called into question.

The stem cell perspective

The other side of cell loss by cell senescence is the production of new cells via stem cell proliferation. It is now recognized that many tissues have the capacity to renew themselves in response to tissue damage and that this can take place at any age. This renewal capacity is the result of resident adult stem cells that have the capacity to proliferate in response to tissue needs.

The concept that stem cells may play a major role in the ageing of critical organs is fairly new.[26] Many of the concepts have emerged from studies in worms, flies and mice, but more data are being accumulated from humans. The importance of stem cells in the function of proliferating tissue such as the haematopoietic system and the gut epithelium is well known. Recently, stem cells have been found in non-proliferating tissues such as the nervous system and muscle. Because of the ease with which it can be studied, the proliferative capacity of the haematopoietic system, which gives rise to immune cells such as T cells, B cells and macrophages, has been shown to decline with age. This plays a major role in the decline of the immune system (see below). The number of neuronal stem cells in the human brain and the number of satellite stem cells in human muscle have also been reported to decrease with age.[27]

The factors that lead to a decrease in stem cell number and function may be the same ones that contribute to cell senescence. These include free radicals, DNA damage and telomere shortening.[26,27] A current line of research is to determine the contribution of intrinsic ageing and systemic factors to stem cell ageing. The decline in stem cell function may not be completely random but may be regulated. Stem cells seem to have distinct ways of maintaining themselves depending on their age.[28] The result of this is that they proliferate less well in older organs. They are also less susceptible to becoming cancerous, which is perhaps a necessary trade-off in older organisms.

The relationship of stem cell ageing to organismal ageing is still unclear. If ageing stem cells result in organ failure due to lack of repair, then they play a major role. On the other hand, stem cell ageing may simply reflect systemic changes that are taking place in the ageing organism. It may even be protective in terms of limiting the chances of uncontrolled proliferation. In any event, the existence of ageing stem cells in many important tissues raises interesting therapeutic possibilities. The first possibility would be that of enhancing the function of older stem cells *in situ* in order to stimulate the repair of older tissue. The second possibility relates to the fact that it is now possible to reprogramme cells such as fibroblasts so that they act like stem cells in that they can differentiate into multiple cell types.[29] Reprogramming of cells may allow the production of individual, personalized stem-like cells for therapeutic purposes. With regard to ageing, this capability raises the questions of whether cells from old individuals can be successfully reprogrammed and whether old individuals can benefit from stem cells from younger individuals.

Systemic components of ageing

Much of this textbook is organized around age-related changes in the various organ systems and their treatment. For example, there is the Gastrointestinal System (Section 2), the Cardiovascular System (Section 4), the Central Nervous System (Section 6) and so on. Many (but not all) of these changes may be the result of changes at the cellular and subcellular levels. A major area of research in the biology of ageing is to describe (as much as possible) the changes at the organ and system levels in cellular and subcellular terms. However, for many years there has been the concept that certain organ systems actually *drive* the ageing process in higher organisms. These include the growth regulatory system, the stress response system, the immune system and the reproductive system. Although they are not the clocks, the ageing of two systems, the neuroendocrine and immune systems, accounts for many of the features of ageing mammals.

The neuroendocrine perspective

Major functions of the neuroendocrine system are stress response, growth regulation and reproduction. These have all been related to biological ageing.[30,31] The clinical aspects of the ageing neuroendocrine system are covered extensively in other chapters of this textbook [see Eating Disorders (Section 1), CNS Disorders (Section 6), Endocrine Disorders (Section 10), etc.].

In the past, the endocrine contribution to biological ageing has been viewed mainly as hormonal deficiency. With ageing, there is a decrease in dehydroepiandrosterone (DHEA) production (adrenopause), a decrease in growth hormone and IGF-1 (somatopause) and a decrease in estrogen and testosterone (menopause/andropause).[30] These decreases were postulated to be driven by the hypothalamus as a sort of 'pacemaker' of ageing. However, biological ageing is more than a hormone deficiency and the idea of a 'pacemaker' is weakened by evolutionary considerations (see above). Because ageing has been viewed as a hormone deficiency, there have been efforts to supplement with things like growth hormone and DHEA, but with limited success. Recently, it has been shown that biological ageing can be modulated substantially through hormonal (growth) pathways even in mammals. This has sparked renewed interest in the insulin signalling pathways apart from their role in diabetes (see below).

One of the hallmarks of ageing is the decreased ability to adapt to stressors. The classical stress response system comprises the hypothalamic–pituitary–adrenal (HPA) axis. The clinical aspects of the ageing HPA axis are addressed in Chapter 97. As would be expected in such a complex system, there are multiple changes in hormone secretion, hormone action, feedback regulation and so on with age.[32,33] For example, the production of DHEA, an important steroid hormone precursor, declines with age despite normal levels of ACTH and cortisol. In general, the stimulation of the HPA appears to increase with age in humans, although there is much individual variation. This HPA stimulation appears to result from a combination of factors. These include repeated external 'life stressors', decreased end organ responsiveness and decreased feedback inhibition. There has been a particular focus on high cortisol levels and their contribution to altered hippocampal function and neurological diseases in the elderly.[32]

There has been renewed interest in the role of the growth regulatory system, comprising growth hormone, insulin and insulin-like growth factors (IGF), in biological ageing.[33] In particular, the insulin/IGF-1 signalling system and its analogues in lower organisms have been studied extensively with respect to its effects on longevity. Modulating insulin/IGF-1 signalling extends longevity in a number of mouse models.[34] The emerging picture is that there are longevity pathways that are conserved across yeast, worms, flies and mammals.[6] These pathways, which normally promote growth, are blunted in times of nutritional stress. In the case of mammals, this would be food shortages in the wild or experimental caloric restriction in the laboratory. These conserved pathways involve insulin-like signalling and other energy-sensing proteins. Inhibiting these pathways with drugs or through genetic manipulation increases lifespan in mice.[35] These same pathways are activated by caloric restriction, which extends maximal lifespan. The mechanism by which these pathways modulate lifespan is under investigation and may involve antioxidant defences.[36] In support of this, the hormone Klotho has been shown to extend maximal lifespan in mice in part by blunting the insulin signalling pathway.[37] Klotho is made primarily in the kidney and also stimulates antioxidant defences. These endocrine studies demonstrate that mammalian lifespan may be manipulated within limits at the hormonal level.

The immune system perspective

A decline in the immune system has been well documented in humans and animal models of ageing. In humans, this results in increased susceptibility to infection, decreased effectiveness of vaccination and an increase in autoimmune disease and possibly cancer.[38] The clinical implications of this are covered in Chapters 46–47 and 115–117.

The function of the adaptive immune system clearly declines with age, but the effect of age on innate immunity is less clear.[39] T cell production declines with age due to the involution of the thymus. The function of T-helper cells declines with age, including decreased expansion and differentiation into effector cells. On the other hand, there is excessive clonal expansion of some subsets of T cells.

This results in decreased numbers of T cells to fight new infections. With regard to innate immunity, there is a similar pattern of a decrease of naïve B cells and a clonal expansion of memory B cells with age. There is also an increase in auto reactive serum antibodies. As with cell senescence, changes in lymphocyte function have been linked to free radicals, DNA damage and telomere shortening, in addition to repeated exposure to antigens such as cytomegalovirus (CMV).[38] There are conflicting reports regarding functional changes in neutrophils, macrophages and natural killer cells.

In societies with good public health measures, the decline in the immune system seems to play a lesser role in human ageing. Even with the involution of the thymus, there is still T cell production in old age and no decline in total peripheral B cell numbers. However, the decline of the immune system may contribute in more subtle ways to the increase in autoimmune disease, cancer and transplant rejection in the elderly.

The biology of ageing and geriatric medicine

Geriatric medicine, as extensively described in this textbook, is daunting in its scope. However, there is reason for hope. First, ageing is not a program for failure but a result of evolutionary neglect after reproduction. As components fail, there is reasonable optimism that they can be fixed or replaced, as is now being done. In this context, the possibility of using intrinsic or extrinsic stem cells to repair organs is exciting.

Second, there is evidence that biological ageing can be altered in fundamental ways even in mammals. These ways include modulation of insulin/IGF-1 signalling (see above) and caloric restriction. Caloric restriction involves feeding animals less food than they would ordinarily eat.[1] This increases mean and maximal lifespan in worms, flies, yeast, mice and rats. It has beneficial effects on almost every aspect of physiological ageing, so it is not clear exactly how it works. These effects include reducing oxidative damage and modulating the insulin/IGF-1 signalling pathway. A recent study showed that caloric restriction delays disease and mortality in monkeys.[40] This has spurred renewed interest in finding a caloric restriction mimetic for humans that would reduce morbidity and mortality without the drawbacks of a restricted diet.

Third, in the light of an ever larger ageing population, biologists who study ageing have realized there is a greater urgency to consolidate a body of knowledge that will be helpful in clinical care. To that end, the National Institute on Aging recently convened a 'Biology of Aging Summit'.[41] The purpose of the meeting was to summarize what is known, identify gaps in knowledge, identify promising new avenues of research and apply some of these concepts to clinical care.

To answer the questions raised earlier, the manifestations of biological ageing will have to be dealt with one condition at a time from the clinical perspective. The pathologies found in each organ and organ system are different. We do not yet know what the underlying link is or if there is one. Even if science were somehow able to affect the biology of ageing in some fundamental way and shift the survival curve (Figure 1.1), there would still be much for physicians to do. There would still be an age bracket where the population suffers a rapid decrease in survival. It would only occur later in life on average. As summarized by Carnes *et al*.,[3] 'Physicians need not fear that science will put them out of work' (p. 698).

Finally, comparative aspects probably give us the best biological perspective of ageing. In lower organisms there is a close relationship between the loss of reproductive capacity and rapid senescence. In humans this is not the case. Humans have the ability to live many years past the end of their reproductive years. Some have speculated that this is because children develop slowly and need long-term parent (and in some cases grandparent) care. In any event, such a long post-reproductive lifespan is unusual, and its length is increasing. From the standpoint of biology, it is a gift – a gift that raises the questions, 'Why do we live as long as we do?' and 'What will we do with the extra time?'.

Key points

- There is no genetic program for ageing.
- Biological ageing varies with tissue and organism.
- There is no one theory of ageing.
- Ageing has both genetic and environmental components.
- Ageing is not the sum of the diseases of ageing.
- Maximal lifespan can vary within limits.
- At the present time, we provide care mostly at the level of the diseases of ageing.

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CHAPTER 2

The demography of ageing

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Introduction

We examine several dimensions of past, current and future demographic changes and the health dynamics of ageing in the USA and other developed countries. Models of the demographic and health dynamics of elderly and oldest-old populations require updating as information about the characteristics of those populations accumulates from (a) demographic sources (e.g. population censuses and vital statistics), (b) specialized longitudinal surveys of elderly populations, (c) epidemiological and clinical studies of elderly subgroups and (d) integrating multiple data sources in comprehensive models of health, ageing and mortality.[1] This last approach will increase in importance with time as the linkage of biomolecular mechanisms with population dynamics becomes increasingly important in assessing the macro/population influences of accumulated knowledge from epidemiological, clinical and basic science studies. This is neither meta-analysis (statistical study of multiple clinical data sets) nor bioinformatics (analyses of laboratory studies to find common patterns). It is a new scientific discipline born of the mathematical integration of medicine, mathematics and biodemography. When populations are successfully modelled at micro (biomolecular), meso (organ systems and individuals) and macro (population) levels, the models can be applied to economic and policy studies – in both government and commercial service (to optimize the effects of medicine and medical research on population health). To understand how these models will evolve, we start with a discussion of the application of basic demographic techniques.

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

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

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

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

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populations. Uncertainty about exact changes in the size and composition of the elderly population is largely due to uncertainty about mortality declines at late ages. Some projections envision larger populations reaching ages 85+ years, for example, 40+ million persons might reach ages 85+ years in 2050 if significant progress in improving known risk factors is assumed.[1]

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

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

Models of chronic disease and mortality trends

The idea that mortality and other age-related health conditions are mutable to late ages (i.e. age 85+ years) is relatively new. The idea that function can be regenerated and the physiological clock run backwards is even newer. In the USA, mortality was thought to have reached irreducible levels by the late 1950s or early 1960s because male survival decreased in that period – although female survival continued to improve. Social Security actuaries assumed that ultimate life expectancy limits would be reached in the United States in 2000 in Social Security Trust fund projections made in 1974. In 2011, the life expectancies of 75.9 and 80.9 years for males and females, respectively, were already 6.3 and 3.8 years above this 'ultimate' limit to life expectancy.

In Table 2.1, we present data on total, male and female life expectancy in 2011.

For the small country Monaco, the total life expectancy of 89.3 years and the female life expectancy of 93.4 years cause one to think the posited ultimate limit to life expectancy of 85 years mentioned above is far too low. The female life expectancy of 85.7 years in Japan and the total life expectancy of 82.3 years also suggest that one should be sceptical about 'ultimate' lifespan limit estimates.

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

Analyses of mortality to late ages suggest why human life expectancy limits are difficult to estimate. First, human lifespans are long (e.g. it will take 120–130 years for a recent, large birth cohort to die out at current mortality levels in Japan, France and other developed countries, making it difficult to acquire reliable data on the full mortality experience of a birth cohort (let alone for multiple birth cohorts). Second, human populations are free living and cannot be studied in experimentally controlled environments. Hence the proportion of human life expectancy potential realized in any population is a smaller, and less certain, proportion of their biological potential than can be observed in animal

Table 2.1 Life expectancy for selected countries in 2011.

	Life at birth (years)						
	Japan	**Monaco**	**Germany**	**France**	**Sweden**	**Canada**	**USA**
Total	82.25	89.73	80.07	81.19	81.07	81.38	78.37
Male	78.96	85.77	77.82	78.02	78.78	78.81	75.92
Female	85.72	93.84	82.44	85.54	83.51	84.1	81.43

Source: CIA, *The World Factbook*, Central Intelligence Agency, https://www.cia.gov/library/publications/the-world-factbook (last accessed 3 October 2011).

models under experimental conditions. Third, for much of human history, fertility was a more dynamic factor than mortality in controlling population growth and shaping population structure. Thus, after large increases in US life expectancy at birth from 1900 to 1950 (i.e. from 47.3 years in 1900 to 68.2 years in 1950, an increase of 20.9 years or 0.42 years of life per calendar year) the rate of increase in life expectancy at birth slowed (e.g. from 68.2 to 70.8 years for 1950 to 1970 or 0.13 years of age increase per calendar year). From 1970 to 2000, life expectancy increased from 70.8 to 77.0 (6.2 years) or 0.21 years per calendar year (a 50% acceleration over the 1950–1970 period), with recent increases accelerating owing to declines in cancer mortality. In the subsequent 11 years, life expectancy increased by only 0.12 years per calendar year, returning to the rate of the 1950–1970 period.

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

For the last 30 years, the centenarian population in the USA and several other developed countries has grown by 7% per year. As higher proportions of larger, more recent birth cohorts survive to late ages, reductions in mortality at those ages will contribute proportionately more to life expectancy gains.

What was observed about health changes in the 1982–1999 National Long Term Care Survey (NLTCS) was remarkable – and contrary to most models of human ageing. In Figure 2.1, we show changes in (a) life expectancy and (b) active life expectancy (ALE) (i.e. period lived free from serious disabilities[2] in 1982 and 1999).

The change in life expectancy was 4.5 years and the change in ALE was 3.8 years. Thus, most (84%) of the gain in life expectancy was in healthy years of life. Figure 2.2 shows the acceleration of the improvement of functioning from age 65 to 100 years.

In Figure 2.2, we can examine rates of change in the difference between ALE and LE in 1982 and 1999. We see that the differences between LE and ALE were similar in 1982 and 1999, never being much higher than 20% (left axis) – although the 1999 differences shifted to the right by

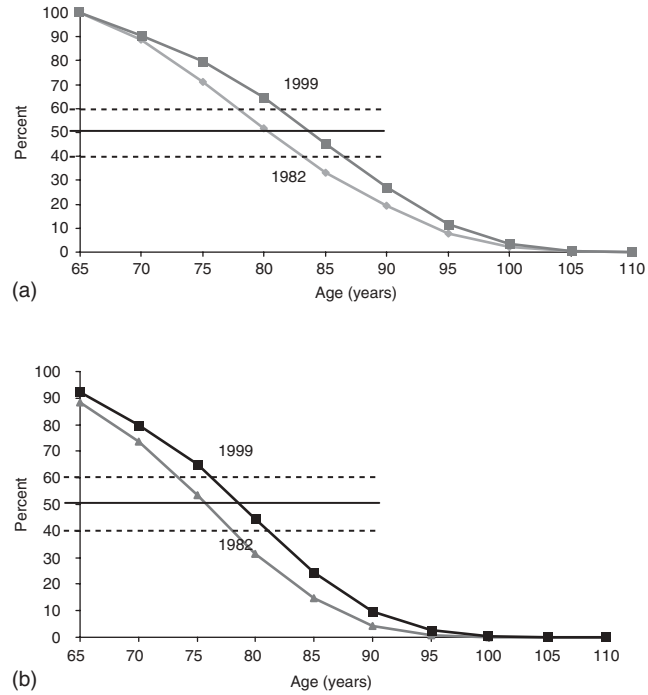

Figure 2.1 (a) 1982 and 1999 life expectancy estimates; (b) 1982 and 1999 active life expectancy estimates.

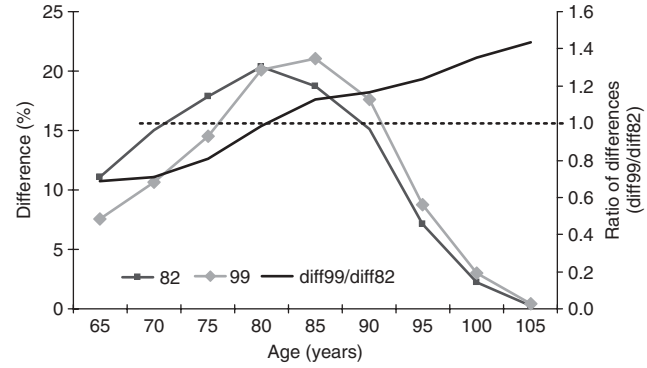

Figure 2.2 Difference between LE and ALE.

about 5 years at age 85 years. Despite higher life expectancy at all ages above 65 years, the difference at age 85 years is only slightly higher than (at age 80 years) in 1982. After age 85 years, the ratio of ALE and LE differences over age suggest a small difference and stable rates of change from 1982 to 1999, up to age 105 years. This is why we can expect future declines in disability and increases in ALE, that is, improvements are manifest to age 105 years.

Further complicating factors in efforts to predict life expectancy are gender and cause-specific differences in mortality. From 1950 to 1970, male life expectancy at 65 years increased by 0.3 years (i.e. from 12.8 to 13.1

years) with life expectancy declining from 1954 to 1968. Female life expectancy increases were 2.0 years from 1950 to 1970 (i.e. from 15.0 to 17.0 years). From 1970 to 2001, life expectancy at 65 years for both US males (13.1 years) and females (17.0 years) increased by 3.3 and 2.4 years – to 16.4 and 19.4 years, respectively. There were larger changes in cause-specific mortality. US age-standardized heart disease mortality declined by 57.8% and stroke mortality by 68.0% from 1950 to 2001. Age-standardized cancer mortality increased by 11.4% up to 1990 but from 1990 to 2001 it declined by over 9%. This decline was due to both social (smoking cessation) and treatment innovation – despite the criticism of the 'war on cancer'. It was suggested that application of 'drug efficiency testing' at the individual level could improve the efficacy of chemotherapy by 20:1.

An area recalcitrant to treatment until recently was neurodegenerative disorders, for example, Alzheimer's disease. Recent analyses of the 1982–1999 NLTCS show large declines in severe cognitive impairment. In 1994 and 1999, severe cognitive impairment was found to map to four ICD9 (Ninth Revision of the International Classification of Diseases) codes. Of these codes, those representing dementia due to circulatory disease (e.g. sequalae of stroke) or mixed processes showed most of the declines, that is, Alzheimer's disease alone was stable.[3,4]

The nature of medical conditions evolved as more persons survived to late ages, for example, up to the 1940s and 1950s much concern was directed to effects of rheumatic fever or syphilis on the heart, hypertension and stroke.[5] In the 1950s and 1960s, hypertensive heart disease declined whereas atherosclerotic heart disease increased. The mean age at which hip fractures occurred in Britain from 1944 to 1990 increased from 67 to 79 years – a 12 years of age increase in 46 years. Concurrently, the nature of hip fractures shifted from intra- to extracapsular fractures. The nature of osteoporosis, the process underlying most US hip fractures, differs from ages 55 to 74 years, where it depends on postmenopausal change in estrogen levels, to ages 75+ years where it is related to age-related effects in the vitamin D endocrine system.

Clearly, more basic physiological processes were at work and over a longer period of time than anticipated by efforts to estimate life expectancy limits based on total and cause-specific mortality trends and by efforts to relate changes to significant, but recent, changes in 'standard' chronic disease risk factors. One study suggested that US stroke mortality started to decline by 1925.[6] Fogel[7] showed that US declines in chronic diseases may be even more long lived. He compared the prevalence of chronic diseases in Civil War veterans age 65–84 years applying for pensions in 1910 (US birth cohorts of 1825–1844) with the prevalence of chronic diseases for WWII veterans over 65 years assessed in the 1985–1988 National Health Interview Surveys (i.e. 1905–1924 cohorts). He found chronic disease prevalence at 65+ years declined by 6% per decade between 1910 and 1985–1988. The prevalence of heart diseases was 2.9 times higher in Civil War veterans aged 65+ years in 1910 than in WWII veterans aged 65+ years in 1985–1988. Declines in chronic diseases set the stage for subsequent declines in mortality up to several decades later.

Fogel[7] attributed changes in chronic morbidity to economic and productive factors affecting early nutrition which increased stature and body mass index (BMI) over time. Many changes between Civil War and WWII veterans predate documented US increases in cholesterol and fat consumption – estimated to have peaked in 1959. One possible explanation of the effects of nutrition on health was the impact of protein, micronutrient and caloric deficiency on fetal development. This was attributed to effects of maternal nutritional deficiencies on the fetal development of organs such that a physiological priority was assumed to exist which dictated which organs received adequate nutrition under conditions of protein and caloric deprivation. If the central nervous system received the highest priority for nutrients, organs such as the liver (affecting cholesterol metabolism and thrombotic factors) and pancreas (affecting glucose metabolism) might be susceptible to developmental restrictions that became manifest in chronic disease risks at later ages. There is evidence for this in studies relating the ratio of placental to birth weight and of weight at 1 year of age to chronic disease at later ages. Higher weight at 1 year was found to be inversely related to ischaemic heart disease, systolic blood pressure and impaired glucose tolerance in adults and possibly to fibrinogen levels in men aged 59–70 years. The relation of systolic blood pressure to placental weight for women and men aged 46–56 years was direct.

Others have suggested that nutritional deficiencies affect persons most at ages where the most rapid physical growth occurs with the highest protein, caloric and other nutrient needs. This is consistent with Fogel's use of the Waaler curve to plot changes in BMI and chronic disease risks.[7] It is also consistent with results that found Japanese male cohorts born 15 years before WWII (i.e. birth cohorts of the early Shāwa period 1925–1939, aged 5–20 years during WWII when there were nutritional shortages in Japan) had elevated mortality from diabetes mellitus, ischaemic heart disease, peptic ulcer, cirrhosis and suicide. These cohort differences in male cause-specific mortality are probably due to poor nutrition during early, critical stages of adolescent male growth spurts. Deficiencies involved gross energy (caloric), proteins and micronutrients; for example, in periods of rapid skeletal growth vitamin D serum levels are highest and vitamin C (affecting collagen formation) and B (affecting methionine metabolism and growth hormone release) needs are elevated.[8]

Two other models may help explain why chronic disease and mortality risks in specific birth cohorts may be related

to nutritional and hygienic factors over long periods of time. One suggests that the effect of viral and bacterial infections on chronic disease has changed over time (in addition to the natural history of the chronic diseases) due to changes in food processing and hygiene. Such arguments have been used to explain why some diseases have strong geographic patterns, for example, association of multiple sclerosis with temperate climates. For atherosclerosis, there is evidence to relate its initiation (i.e. injury to arterial endothelium starting inflammatory and wound-building activity stimulated by dietary cofactors such as serum cholesterol and aggravating conditions such as hypertension) to viral and bacterial insults. This model derives support from evidence that atherosclerotic plaques have a monoclonal origin, suggesting that a somatic mutation is involved in plaque initiation.[9] Various infectious agents have been found in plaques or in circulating immunological complexes in cases with circulatory disease versus controls. Among agents implicated are *Chlamydia pneumoniae*, CMV (cytomegalovirus)[10] and other herpes viruses. One mechanism that could be involved in infectious agent damage to arterial endothelium involves platelet-derived growth factor (PDGF). PDGF may play a central role in atherogenesis because it is both a mitogen and a chemoattractant. There is a striking homology (87%) between the amino acid sequence of PDGF and a protein from an oncogene (v-sis) in the simian sarcoma virus. This homology suggests that PDGF is important in the proliferation of cells transformed by a virus. Cells transformed by retrovirus, DNA viruses and cells with somatic mutations appear to secrete PDGF molecules. Cells virally transformed appear to express a previously repressed cellular gene (c-sis) for PDGF. An immunological factor identified as raising the risk of myocardial infarctions, especially for males, is null allele C4B*Q0. There is evidence to suggest that immune mechanisms are involved in hypertension, with some data pointing to predisposing genes in the major histocompatability complex, either secondary to hypertension-induced vascular damage (causing positive feedback in plaque growth) or as a primary abnormality. However involved, reductions in infectious disease exposures might reduce hypertension prevalence in recent cohorts.

Data from Hiroshima suggest that ionizing radiation is another exogenous stressor involved in hypertension and cardiovascular disease. In Hiroshima, there was acute γ-radiation. In Chernobyl, the most damaging radiation was β (electrons) due to biological incorporation of ^{90}Sr in bone and ^{137}Cs in soft tissue. The radiation flux of these isotopes is relatively high although they have a long half-life of about 30 years. With this type of radiation, there appears to be an acceleration of basic age processes[3] consistent with the well-known free radical theory of ageing. This syndrome involves cataracts, stroke, circulatory diseases and neurodegeneration. Effects on neurodegeneration originally were not viewed as plausible because it was believed neurons seldom divided. There is now evidence that neuronal regeneration occurs in several areas of the brain (e.g. in the hippocampus and the substanta nigra), as the brain is an area of high metabolic activity where baseline free radical production is high and where protein formation in synaptic gaps is sensitive to even very low doses of radiation.

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

To explain how infectious disease involvement with atherosclerosis relates to long-term population health and mortality changes, Mozar *et al*.[10] suggested that changes in circulatory disease risk can be traced back at least to 1910, when 8% of US deaths were attributed to heart disease. This proportion rose to 30% by 1945 and to 54% by 1968. A similar trend occurred in the UK. with diseases of the heart and blood vessels responsible for 11.4% of all deaths in 1910, rising to 36.3% in 1959. In the USA, the peak heart disease risk was reached in 1968. A caution is that death certificates are notoriously inaccurate as to the cause of death. Mozar *et al*.[10] suggested that this was due to ingestion of atherogenic viruses during the pre-War period (i.e. initial injuries led to processes with lengthy latency times; autopsy studies found that fatty streaks and plaque development began at early ages, possibly as early as age 3 years in the aorta, even in less developed countries where heart disease risks do not increase late in life), which interacted with increased fat consumption and other risk factors (e.g. the methionine–homocysteine model of atherogenesis) up to 1970.

The nutritional (hygienic) factor argued by Mozar *et al*.[10] to be associated with declines in heart disease risk was commercial food processing – initiated before the turn of the century. The use of commercial food processing accelerated after WWII as economic conditions improved, large proportions of the US population moved from rural to urban areas and efforts to control livestock infections such as vesicular xanthema (a viral disease of swine discovered in 1932) were started, for example, in California in 1945–1949. An

outbreak of vesicular xanthema in 1952 mandated thermal preparation of food fed to swine. A hog cholera eradication programme began in 1962. The Swine Health Protection Act was passed in 1980.

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

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

Cancer risks are now decreasing in the USA. It has been proposed that common processes underlie both cancer and ageing. Warner *et al*.[11] related these processes to effects of caloric restriction (CR) on programmed cell death (PCD). They suggest that CR upregulates the expression of antioxidant genes and attenuates the formation of reactive oxygen species – and possibly DNA and mitochondrial damage caused during ageing. The emphasis on effects of antioxidants on ageing and cancer leads to a third model of changes in chronic disease risks and their contribution to late-age health changes.

Another hypothesis is that long-term changes in micronutrients alter chronic disease risk. Antioxidant vitamins A, C and E seem to affect cardiovascular disease by lowering the potential for LDL cholesterol to become oxidized, consumed by macrophages and trapped in atherosclerotic plaques as foam cells. Vitamins A and E are redifferentiating agents that repair some genetic damage and antioxidants preventing certain chemical reactions from causing somatic mutations or other cell damage. However, it is vitamins and antioxidants as components of food that produce this effect, not as drug supplements.

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

Vitamin D supplementation in milk and other foodstuffs has been adopted for a long time in the USA and Canada. One strategy to examine its effects on chronic disease is to trace the epidemic of atherosclerosis and ischaemic heart disease and the ratio of male to female deaths. In the USA, this ratio was ~1 until the mid- 1920s, then the male predominance in ischaemic heart disease increased steadily until 1968. Curative effects of cod liver oil on rickets were documented in 1917. In 1923, the USA imported 0.5 million gallons of fish liver oil and in 1930, 2.8 million gallons. UV-irradiated milk was introduced in the USA in 1924. Manufacture of vitamins D_2 and D_3 increased from 35 lb in 1948 to 14 000 lb in 1972. By 1970, vitamin D_2 was added to many food products. There was a concurrent decline in Mg in the US diet. Mg mediates effects of vitamin D on cellular calcium absorption. Vitamin D hypervitaminatosis interferes with Mg absorption. Oversupplementation of vitamin D aggravated Mg deficiencies in the US diet. Mg deficiency may have additional effects on circulatory disease because it appears to stimulate renin release through the elevation of prostaglandins; and suppress aldosterone production by mobilizing intracellular calcium.

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

The sex ratio of femoral neck fractures was used to trace the origins of the US osteoporosis epidemic. This ratio suggests (based on Rochester, MN, data) that osteoporosis began its upsurge in the late 1920s – about the same time as ischaemic heart disease began to increase. Vitamin D intake, its increase from 1920 to 1970 and its subsequent decrease could explain the interaction of atherosclerosis and osteoporosis for females and their joint trajectories. This is further aggravated by the use of sunblock, leading to a

decrease in endogenous vitamin D production. Vitamin D increases Fe absorption, which may lead to increased free radical generation and oxidation of LDL cholesterol. This might explain the rapid increase in atherogenesis in females postmenopausally, that is, Fe stores in females increase and, with excess vitamin D, increase calcification of atherosclerotic plaques.

Another model for explaining long-term trends in circulatory diseases is the homocysteine theory.[8] Ingestion of the sulfur-based amino acid methionine (an essential amino acid for mammalian growth) produced, after demethylation, homocysteine. Elevated levels of homocysteine, due to genetic predisposition or dietary deficiency of vitamins B_6 and B_{12}, had toxic effects on arterial endothelium. Lesions created by elevated homocysteine levels showed the characteristic fibrous nature of atherosclerotic plaques – but not with lipid deposition if cholesterol is not elevated. The theory suggests that fibrous plaques are not produced unless vitamin B deficiency allows the accumulation of homocysteine and a toxic metabolite, homocysteine thiolactone. The metabolism of homocysteine is affected by vitamin C. Although ascorbic acid is a potent reducing agent, after oxidative conversion to semidehydroascorbic acid its physiological function is to oxidize the sulfur atom in homocysteine. Three stages for methionine utilization are (a) demethylation and dehydration of methionine to homocysteine thiolactone, (b) oxidation of homocysteine thiolactone to homocysteic acid by semidehydroascorbic acid and (c) reaction of homocysteic acid with ATP (adenosine triphosphate) to form active coenzymes to synthesize sulfate esters of connective tissue proteoglycans.

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

The relation of this mechanism to increased heart disease in the twentieth century may be due to an increased dietary ratio of animal to plant protein (dietary intake of methionine is correlated with cholesterol intake). This may explain the relation of increased body size with atherosclerosis. Vitamin B_6 levels decrease through life to the eighth decade because serum glutamine oxaloacetic transaminase activity decreases. When the elderly are treated with pyridoxine, transaminase levels return to levels of younger persons.[12] Also, since pyridoxine is water soluble, as the lipid content of the diet increases, pyridoxine availability may decrease.

To explain US population trends in heart disease, quantities of synthetic pyridoxine hydrochloride were examined.[8] US production increased from 1900 kg in 1944 to 30 000 kg in 1963. Imports increased from 9100 kg in 1963 to 17 700 kg in 1969, to 59 500 kg in 1972 (yielding a threshold consumption of 0.79 mg per day) and to 275 000 kg in 1978 (3.42 mg per day). This increase is consistent with post-1968 declines in coronary heart disease. Since vitamin B_6 supplementation will prevent arterial damage, but not reverse it, the decline in circulatory disease should increase as younger cohorts who had adequate supplementation reach older ages. Supplementation is also necessary because thermal food processing (which may have decreased viral exposures in animal protein) degrades natural pyridoxine. This is controllable by consuming adequate synthetic vitamins B_6 and B_{12}.[12] The problem increases with age due to altered vitamin intake, absorption or metabolism.

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

New explanations of these processes derive from a better understanding of cellular bioenergetics – especially the function of the mitochondria. This suggests that, in addition to the CR model, they are the effects of thyroid hormone on mitochondrial function. It is known that thyroid hormone administration increases oxygen

consumption by mitochondria. The effect may be both short and long term. The short-term influence (within minutes of the hormone treatment) results in enhanced expression of the mitochondrial genome. Thyroid hormone increases levels of mitochondrial transcription by elevating mRNA synthesis and improving their stability. The long-term influence (after 24 h) involves the stimulation of mitochondriogenesis. This may explain why honey bees, with a nutritional intervention (royal jelly) containing a protein with partial structural similarity to human thyroid hormone, may stimulate the production of cytochrome *c* in mitochondria with lifespan epigenetically increased 30-fold or more despite elevated metabolic rate. Intervention effects were shown in mice where the mitochondrial function of old mice was returned to that of young mice by administration of α-lipoic acid (an antioxidant zwitterion) and L-acetylcarnitine, an agent stimulating fatty acid metabolism.

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

To make the ebb and surge of specific chronic diseases over time consistent with the models described above, there had to be changes, not only in mortality at late ages, but also in the nature of age-related chronic disease processes over the past 150 years as nutrition (both macro- and micronutrients), food hygiene (e.g. *H. pylori* infections, toxins due to food spoilage) and viral and bacterial exposures changed. Changes may also affect the expression of genetic diseases by altering gene–environment interactions or by changing the inflammatory response of the host to stress, for example, altering serum levels of IL-6.[13] The average health characteristics of the very elderly population may evolve in the future as different cohorts, with different early health experiences, enter this age group. As the profile of chronic diseases affecting elderly populations changes over their lifespan, one also is aware of long-term changes in age-related chronic disease – and in ageing changes.

Mortality selection and trajectories

Hygiene and nutritional changes caused differences in chronic disease risks across birth cohorts, and these and other factors (e.g. smoking) may have altered age trajectories of cohort mortality. Specifically, many demographic models use a Gompertz function to describe age increases in mortality. However, at late ages the trajectory of human mortality deviates from the Gompertz curve, overpredicting increases in mortality.[14]

One explanation for deviations from the Gompertz curve (beginning about age 85 years) is mortality selection. For example, the prevalence of the B gene of the fourth component of complement (C4B*Q0) is a risk factor, in men, for myocardial infarction. The prevalence of this gene dropped for males in the fifth and sixth decades of life due to adverse affects on longevity. Its prevalence declined at later ages in females. In Italian centenarians there were decreased thyroid autoantibodies compared with persons in their 80s.[15] The prevalence of the ApoE-4 genotype in Finnish centenarians was lower than that at earlier ages. In lung cancer, genetic susceptibility involves the cytochrome P450 enzyme system. The proportion of genetically related lung cancer cases declines sharply between ages 50 and 70 years. In Swedish twins,[16] the relative risk of CHD (congenial heart disease) mortality declined from 14:1 to 15:1 in mid-age to 1:1 above 85 years of age. Thus, many studies of genetically controlled diseases showed change in genotype prevalence due to mortality selection. In clinical examinations of long-lived groups, health at late ages (e.g. 80+ years) is often better than for persons, say, aged 70–79 years.[17]

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

As a consequence of selection, whereas human mortality rates increase by 8–10% per year in middle age, the rate of mortality increase at late ages is slower. In seven studies where mortality was observed up to ages 100+ years, rates increased an average of 3.1% per year between ages 100 and 110 years.[14] For US males, cohort mortality reached a high constant level at ages 100–110 years. US female cohort mortality increased by 3.0% per year of age from 100 to 110 years. The average US cohort mortality rate at age 110 years was 41%; the average for the seven studies was 45%.[14]

The 1982–1999 NLTCS data show this plateau. We examined an alternative model where a plateau is due not only to a genetically heterogeneous population, but also to a balance of degenerative and regenerative physiological processes. This suggests that engineering reliability models, such as the Weibull distribution, are not sufficient in that they describe failure in a homogenous system – not a complex heterogeneous system. It is no longer sufficient to describe a plateau as a genetically determined trait but as a

temporally (absolute clock-time – not simply age) changing equilibrium of decay and repair functions.

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

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

From 2035 to 2050, the US centenarian population is expected to grow to 0.6 million persons. The US population aged 95+ years in 2050 would be 3.8 million persons. The population aged 85+ years would be 18.9 million persons – or 4.8% of the US population. The population aged 65+ years would be 20.4% of the total US population. These are 'middle' range projections. Alternative series, assuming greater life expectancy increases, project 2.6 million centenarians in 2050 with 26.4 million persons aged 85+ years and 93.1 million aged 65+ years, or 0.63, 6.4 and 22.7%, respectively of the total US population (i.e. based on life expectancy at birth in 2050 of 83.8 versus 91.1 years for males and females, respectively; the intermediate assumption was 79.7 and 85.6 years for males and females. respectively. in 2050). Second, for individuals at late ages one will have to use different estimates of life expectancy than are available from actuarial estimates.[2] This could change calculations for assessing cost-effectiveness of specific medical interventions at late ages.

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

Discussion

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

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

Better evaluations of the efficacy of treatments at late ages are needed. Surgical interventions in patients aged 90–103 years have been shown to have become less hazardous – intraoperative mortality dropped from 30 to 8% over 30 years. As pacemakers increase in sophistication, their use in elderly patients improves outcomes. Dual-chamber, demand-driven pacemakers may be particularly useful for the elderly because of increased reliance with age on atrial function for cardiac output. There are interventions with low mortality that increase the function of elderly persons. Hip and knee replacements are in this category, and also plastic lens implants for cataracts.

Hence the cost–benefit ratios of medical procedures at late ages may be underestimated because the life expectancy of individuals at late ages and the amount of functional capacity that can be regained are underestimated. A reason may be that trends in disability and mortality among populations with particular health characteristics may not be correctly represented in evaluations of patients for the medical and surgical procedures now available for elderly populations. Certain situations, such as long waiting periods for 'elective procedures' in some European healthcare systems, may have more adverse effects at late ages than

in younger populations and operate as a 'self-fulfilling' prophecy about limitations to late-age interventions. Such problems will emerge increasingly in the future as the number of very elderly persons increases and prior health histories evolve. One factor to which recent changes in disability may be related is education. Education has been projected to improve with the proportion of persons aged 85–89 years with less than 8 years of schooling declining from 60+% in 1980 to 10–20% by 2015. A number of health behaviours are associated with education and also the risk of dementia.

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

Key points

- Vitality determines mortality and fertility.
- Vitality links birth–death processes.
- Vitality is driven by mitochondrial function under thyroid control.
- Free radical chemistry is central to cellular bioenergetics.

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CHAPTER 3

The physiology of ageing

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

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

Ageing of organs

Ageing of the skin

The skin is the largest organ of the body and has many important functions. It functions as a mechanical barrier, regulates temperature, initiates immunological functions, communicates external stimuli to the body and protects against the effects of ultraviolet light. The skin is composed of three major layers: the outermost layer is the epidermis, followed by the dermis, which leads to the hypodermis. In the epidermis, a multitude of cells exist such as keratinocytes, melanocytes, Langerhans cells and Merkel cells. The basement membrane separates the epidermis from the dermis. The dermis is composed of connective tissue, consisting mainly of collagen fibres, and elastin. The fibroblasts are the major cell type. The hypodermis is composed of the adipocytes, and also the intravascular bundle. The typical signs of ageing include wrinkling and sagging of the skin. Extrinsic ageing is more prominent in the highly vascular retina unlike the lens, and it has six neural cell types organized in 10 layers. The photoreceptor cells (rods and cones), and the retinal pigment epithelium (RPE) are most affected with ageing.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Intrinsically aged skin is thin, pale, and finely wrinkled. Histological staining shows flattening of the dermo–epidermal junction. This form of ageing is felt to be secondary to superoxide free radical formation. Aged skin demonstrates a reduced keratinocyte proliferative capacity. The number of epidermal cell layers remains unaltered during ageing (Table 3.1). A decrease in melanocytes contributes to the paling of the skin.

The dermo-epidermal junction flattens with age due to the retraction of the epidermal papillae (Table 3.2), which leads to a skin structural unit that is less resistant to shear forces than is younger skin. Skin thickness tends to decrease after the seventh decade.[1] Within ageing skin, increased vasoconstrictor responses and decreases in both vasodilators and vasoprotective agents have been demonstrated, and atrophy and hypertrophy of the subcutaneous tissue are common in aged individuals.

The repair of physical damage is an essential day-to-day function of skin. Alteration in wound healing may lead to chronic ulceration and non-healing. The dysfunction of dendritic cells leads to the formation of skin neoplasms. The decrease in the protective effect of the skin leads to further loss of protection from UV light. Sunlight is also felt to lead to the generation of oxygen radicals leading to ageing. It has been shown *in vitro* that keratinocytes and dermal fibroblasts from habitual sun-exposed sites have shorter life spans.

In summary, the skin is the major barrier for our body to protect us within the environment (Table 3.3). As the ageing process ensues, cellular functions are altered, leading to problems with wound healing, immunosurveillance, temperature regulation and general barrier functions.

Table 3.1 General effects of ageing on the cell types resident within the skin.

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

ECM, extracellular matrix

Table 3.2 General effects of ageing on the function of individual components of the skin.

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

Table 3.3 Summary of age-associated changes in skin function.

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

Skeletal muscle ageing

Skeletal muscle comprises 40–50% of the human body and is composed of muscle tissue, nerve tissue, blood vessels and connective tissue. Myoblasts are precursor cells, which fuse together forming bundles of muscle fibres. There are two types of individual muscle fibres: type I or slow twitch and type II or fast twitch. Type II has two components: type A are called *fast-oxidative fibres*, and type B are known as *fast-glycolytic fibres*. With ageing, there is a shift towards type I fibres.[2] There are several types of muscle contractions: shortening contractions, isometric contractions and lengthening contractions. Skeletal muscles have developed adaptive responses to the generation of reactive oxygen species to protect themselves from oxidative damage.

These age-related changes in muscle mass are termed *sarcopenia* and lead to an age-related decrease in muscle strength and power. The basal metabolic rate of muscle decreases by 4% per year after the age of 50 years. The synthesis of myosin heavy chains declines with age, whereas the sarcoplasmic protein pool is unchanged.[3,4] The regenerative potential of skeletal muscle, and overall muscle mass, decline with age. There is an increased infiltration of fat into muscle with ageing. Some of the ageing changes are due to the decrease in physical activity that occurs with ageing.

During senescence, there is a loss of motor neurons and muscle fibres. The loss of motor neurons is of primary

importance because it is likely to be the main reason for loss of muscle fibres. Electrophysiological studies have demonstrated a reduced number of motor units in old muscle.[5] The size of the average motor unit increases with age. The loss of strength does not result from failure of the central nervous system to activate motor nerves; however, a reduced rate of firing of motor nerves during maximum voluntary contraction in older subjects may limit the maximum force production in some muscles.[6] During a sustained contraction, central fatigue may be more common in older adults than in younger persons. Age-related fibre atrophy generally is restricted to type II fibres, at least in the muscles of the leg, and this selective atrophy is important functionally because type II fibres can generate more power than type I fibres. It is unclear whether there is impairment in the release of calcium affecting the rate of relaxation and contraction. Welle *et al*. have shown that older human muscle has reduced expression of several mRNA's encoding proteins involved in mitochondrial electron transport and ATP synthesis.[7] An accumulation of DNA deletions is seen in mitochondria of skeletal muscle with age.[8]

With ageing, changes occur with skeletal muscle, affecting size, strength, endurance and functionality in the elderly (Table 3.4).

The ageing eye

Multiple population-based studies have shown a significant increase in the prevalence of impaired vision with advancing age.[9] As such, visual impairment is negatively associated with the independence and functional status of elderly people.[10] In addition, impaired vision may negatively affect cognitive functions among the elderly.[11] The eye suffers age-related disease and is affected by many systemic illnesses (see Chapter 85, Disorders of the eye). The eye consists of the retina, lens, cornea and a neurovasculature. The lens is a transparent, avascular tissue contained within a capsule. The lens cells divide, but are not shed, and as a result, the lens continues to grow throughout life. It has defence mechanisms from reducing compounds that can cause damage. Aggregation of proteins is thought to be responsible for the yellowing of the lens and also the increase in light scattering. Glutathione, a key protecting molecule in the lens, tends to decrease with ageing. Crystallins are proteins that provide the high refractive index of the lens. Alterations in structure and increased aggregation of these proteins are noted with ageing. Cataract formation increases with ageing and a multitude of enzymes have lowered activity in a cataract.

The retina is the light-responsive part of the eye and its density decreases with ageing. There is also loss of ganglion cells and RPE. Lipofuscin is a protein that is formed through many mechanisms and its accumulation can cause cell death in cell culture.[12] Age-related macular degeneration (AMD) is the major cause of non-preventable blindness in Western countries and its prevalence increases with ageing. The molecular pathway leading to AMD has not yet been elucidated. There are also age-related changes to the sclera where it is thinner, yellower and less elastic. Light scattering appears to increase through the cornea with ageing. The vitreous body tends to liquefy with age and collagen fibres concentrate.

Table 3.5 summarizes the changes that occur with ageing affecting the functionality and cognitive capabilities of elders.

The ageing cardiovascular system

Ageing is associated with complex and diversified changes in cardiovascular structure and function. Changes occur at the structural/functional levels and also the molecular/cellular level. The heart becomes slightly hypertrophic and hyperesponsive to sympathetic (but not parasympathetic) stimuli, so that the exercise-induced increases in heart rate and myocardial contractility are blunted in older hearts. The aorta and major elastic arteries become elongated and stiffer, with increased pulse wave velocity, evidence of endothelial dysfunction and biochemical patterns resembling atherosclerosis. These changes are thought to be caused by increased angiotensin II activity in the arterial wall,[13] which leads to endothelial dysfunction, vascular smooth muscle proliferation and an increase in glycation and collagenization. Molecularly these changes are secondary to an increase in transforming growth factor beta-1

Table 3.4 Summary of age-related changes in muscle.

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

Table 3.5 Changes in vision with ageing.

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

(TGF-β1), matrix metalloproteinase type II, calpain 1 and milk fat globule EGF-8. There is also an increase in reactive oxygen species reactivity, which leads to a decrease in endothelial nitric oxide bioavailability. The arterial baroreflex is altered in ageing, with the baroreceptor of the heart showing greater impairment than the baroreceptor control of peripheral vascular resistance. No conclusive evidence has been shown that alterations in afferent, central neural, efferent and effector organ portions of the reflex arch are altered with ageing. Reflexes arising from cardiopulmonary vagal afferents are blunted in aged individuals.

The changes that occur in the aged heart are outlined in Table 3.6. It is important to clarify that all these changes in cardiovascular function do not imply failure of the system and, in the absence of overt cardiovascular disease, do not result in symptoms.

The ageing immune system

The function of the immune system declines with age (Table 3.7), which leads to an increased frequency of infections, increased prevalence of neoplasms and autoimmune disorders. Thymic involution is a hallmark of ageing, although there are thymic independent pathways for the development of the immune system. Response to vaccines is also decreased. The ability of haematopoietic stem cells to replicate decreases with ageing.[14] There is a decrease in haematopoietic stem cells of the lymphopoietic heritage with progressive predominance of myeloid-biased clones, and this imbalance is responsible for the increase in myelodysplastic syndromes with ageing. All cells are not affected similarly by ageing so, for instance, memory CD4 T cells retain function whereas naive CD4 cells lose function.

There is an age-dependent alteration to antigen-presenting cells. Certain cytokines increase with ageing, such as: (1) interferon γ, (2) TGF-β, (3) tumour necrosis factor (TNF), (4) IL-6 and (5) IL-1, which can lead to dysregulation of haematopoiesis. Most tests of T-cell function are depressed in elderly individuals.[15] They tend to secrete less IL-2 after being stimulated by antigen-presenting cells. Several studies have suggested a positive association between good T-cell function *in vitro* and individual longevity,[16] and between absolute lymphocyte counts and longevity.[17] A high proportion of centenarians have relatively well-preserved immune functions compared with the less elderly.[18]

Monocytes have also been shown to have decreased function with ageing (Tables 3.8 and 3.9). Natural killer cell numbers increase with ageing, but NK cytonicity as measured on a per cell basis decreases. The cytokines produced by activated NK cells (rRANTES and IL-8) also decrease with ageing.[19]

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

The ageing pulmonary system

The ageing lung closely mimics changes in lung tissue that are associated with disease process such as emphysema (Table 3.10). Senile hyperinflation is a well-recognized entity. There is an increase in airspace size, stiffening of the chest wall, loss of respiratory muscle strength, a decrease in intervertebral spaces and a decrease in elastic recoil of the lung tissue. Diaphragmatic strength declines with ageing, which predisposes diaphragmatic fatigue. These changes result in age-related declines in the lung volumes and flow rates affecting the forced expiratory volume (FEV1)

Table 3.6 Effects of normal ageing on the cardiovascular system.

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

Table 3.7 Changes in immune system function with age.

Decreased cell-mediated immunity
Lower affinity antibody production
Increased autoantibodies
Decreased delayed-type hypersensitivity
Decreased cell proliferative response to mitogens
Atrophy of thymus and loss of thymic hormones
Increased IL-6
Decreased IL-2 and IL – 2 responsiveness
Decreased production of B cells by bone marrow
Accumulation of memory T cells (CD-45)
Impaired macrophage function
Facilitated production of anti-idiotype antibodies
Increased NK cell number but decreased cytotoxicity

Table 3.8 Changes in T cells with age.

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

Table 3.9 B cell changes with ageing.

Surface MHC[a]class II molecule expression
Proportion of cells capable of clonal expansion
Number of bone marrow precursors
Number of T cell-dependent antibody-forming cells
Potency
Antibody efficacy

[a]MHC, major compatibility complex.

and the forced vital capacity (FVC).[20] The PaO_2 decreases progressively and linearly, falling from ~95 Torr at age 20 years to about 75 Torr at age 70 years. The alveolar dead space increases whereas the pulmonary diffusing capacity decreases progressively and linearly with age, falling by ~20% over the course of adult life. The ventilatory responses to both hypoxia and hypercapnia have also been shown to decrease with age.

The ability to exercise, as indicated by the maximum oxygen uptake ($VO_{2\,max}$), also decreases linearly and progressively, falling by ~35% between the ages of 20 and 70 tears. The alveolar ducts also enlarge, resulting in decreased surface area. Older persons have a 50% reduction in the response to hypoxia and a 40% reduction in response to hypercarbia.

Table 3.10 Changes of the pulmonary system with ageing.

Decreased FEV1 and FVC
Increased residual volume
Cough less effective
Ciliary action less effective
Ventilation–perfusion mismatching causes PaO_2 to decrease
Trachea and central airways increase in diameter
Decreased lung mass
Decreased respiratory muscle strength
Decreased diffusion of carbon monoxide
Decreased maximum inspiratory and expiratory pressures
Chest wall stiffens
Decreased diaphragmatic strength
Decreased ventilatory response to hypoxia and hypercarbia
Decreased antioxidants

Immunological changes with ageing include an increase in neutrophils and a decline in the percentage of macrophages with ageing in brochoalveolar lavage fluids. IgA and IgM levels also increase and the ratio of CD4+ to CD8+ lymphocytes increases.[21] Older persons have an increased response to bronchial constrictors and a poorer response to beta-receptor agonists, due to a reduction in beta-receptor affinity with ageing. Older persons have a limited response to cysteinyl leukotriene receptor antagonists.

The ageing nervous system

The nervous system is composed of a multitude of cells and layers that control many aspects of function such as memory, speech, verbal and visual function and sensory and motor functions. There are great variations between individuals (Table 3.11).

Both normal senescent age-related changes and late-onset diseases of the brain produce a decline in performance. The number of contacts and the total surface area of the synapses decrease significantly and their average synaptic size increases to different extents according to the brain area taken into account. Pre- and postsynaptic elements thicken with age, whereas vesicle size decreases (Table 3.12). There is failure of the chemical transmission process with ageing.[22]

The regulation of calcium influx is essential to pre- and postsynaptic events. Tanaka *et al*.[23] showed that reduced calcium influx with ageing might cause the reduced acetylcholine release by aged synapses. Brain ageing is also associated with oxidative damage and low energy

Table 3.11 Changes in the central nervous system with ageing.

Small decrease in brain mass
Decreased brain flow and impaired autoregulation of perfusion
Proliferation of astrocytes
Decreased density of dendritic connections
Increased numbers of scattered senile plaques and neurofibrillary tangles
Decreased myelin and total brain lipid
Altered neurotransmitters including dopamine and serotonin
Non-random loss of neurons to modest extent
Increased monoamine oxidase activity
Decrease in hippocampal glucocorticoids receptors
Slowed central processing and reaction time

Table 3.12 Age-related changes in the pre- and postsynaptic markers of the striatal dopamine synapse.[22]

Parameter	Change
Presynaptic markers	
Tyrosine hydroxylase immunoreactivity	↓
Tyrosine hydroxylase activity	↓
Dopamine (DA)	→ / ↓
DA turnover	→ / ↑
Cold stress-induced DA turnover increase	↓
Reserpine-induced DA turnover increase	↓
DA turnover increase induced by training in reaction time	↓
Postsynaptic markers	
D1 receptor levels	↓ / →
D2 receptor levels	↓
D1 receptor turnover	↓
D2 receptor turnover	↓
Adenylate cyclase activity	↓
cAMP-induced phosphorylation	↓
DA/cholecystokinin receptor interaction	↓
D2 denervation supersensitivity	↓

metabolism[24] and nitric oxide has cytotoxic action on neurons.[25] Adrenal glucocorticoids have been shown to accelerate age-related damage in the hippocampus, because of their ability to compromise energy metabolism and make neurons more vulnerable to glutamate excitoxicity.[26]

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

In summary, the ageing nervous system has many features that affect individuals in a wide variety of ways (Table 3.13). For functional changes, such as cognition, these appear to peak before the age of 30 years.

Table 3.13 Age-related changes in the peripheral nervous system.

Loss of spinal motor neurons
Decreased vibratory sensation, especially in feet
Decreased thermal sensitivity
Decreased sensory nerve action potential amplitude
Decreased size of large myelinated fibres
Increased heterogeneity of axon myelin sheaths

Table 3.14 Changes in calcium homeostasis with age.

Parameter	Change
Serum calcium	No change
Intestinal calcium absorption	↓
Serum parathyroid hormone	↑
Serum 1,25(OH)2D	↓or no change
Resorption of calcium from bone	↑
Net calcium balance	↓

The ageing skeleton

Almost everyone loses bone with ageing (Table 3.14). Women have acceleration of bone loss with onset of menopause. Men lose bone more slowly, and lose cortical bone only as they lose tissue in general, not preferentially, as is the case in women. Both men and women lose trabecular and cortical bone. Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, which increases the susceptibility to fracture. Remodelling of both cortical and trabecular bone takes place through sequences of activation, resorption (by osteoclasts) and formation (by osteoblasts). A multitude of hormones regulate bone remodelling: (a) calcitriol, (b) parathyroid hormone (PTH), (c) sex steroids, (d) calcitonin and (e) insulin-like growth factors (IGF-1, IGF-2). Vitamin D and PTH maintain serum calcium. Serum calcium levels do not change with age, but the way in which they are maintained changes dramatically.

With increasing age, serum calcium levels are increasingly maintained by resorption of calcium from bone rather than resorption from the diet. The decreased sensitivity of the parathyroids to calcium, decreased responsiveness of the kidney to PTH, and decreased responsiveness of the intestine to calcitriol [1,25-dihydroxycholecalciferol, 1,25(OH)2D] all work together to increase serum PTH levels with age. Calcium supplementation is effective in lowering PTH levels and reducing bone loss in the elderly.[27]

The ageing gastrointestinal tract

The digestive tract maintains much of its normal physiological function during the ageing process. There

are a number of physiological changes that occur with ageing that have the potential to influence drug deposition and metabolism and may influence gastrointestinal (GI) function.

Pharyngo-oesophageal function changes with age, but the clinical significance is unclear. In elderly individuals, a decrease in the number of myenteric ganglion cells per unit area along with a thickening of the smooth muscle layer has been described. Age has no effect on peristaltic velocity, basal lower oesophageal sphincter (LES) pressures or frequency of 'abnormal' double- and triple-peaked waveforms. Gastric emptying for large, but not small, volumes is reduced in the elderly, gastric acid levels are increased, the incidence of peptic ulcer disease is known to increase and gastroduodenal mucosal prostaglandin levels decline with ageing. Changes in small bowel motor patterns with ageing have been described, including relatively minor effects on small bowel manometric patterns with decreased frequency of contractions after eating, reduction in the frequency of the migrating motor complex and reduced frequency of propagated clustered contractions.[28] The physiological and clinical consequences of these changes are uncertain. The absorption of nutrients by the intestinal tract depends on a multitude of factors. Highly lipid-soluble compounds such as vitamin A show increased absorption whereas vitamin D is decreased. Fat absorption is decreased whereas cholesterol is increased. Carbohydrate absorption has been shown to decrease in rats. Numerous studies have assessed sigmoid functioning and colonic transit, and there is little evidence of any alteration in these measures in older adults.[29]

In summary, physiological changes of the GI tract are primarily preserved, although changes do occur that have clinical consequences (Table 3.15). Loss of enteric neurons

Table 3.15 Changes in the GI tract with ageing.

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

Table 3.16 Changes in the renal system with ageing.

Decreased creatinine clearance and GFR[a] 10 ml per decade
Decrease of 25% in renal mass
Decreased sodium and potassium excretion and conservation
Decreased concentrating and diluting capacity
Decreased serum renin and aldosterone
Accentuated ADH[a] release in response to dehydration
Decreased nitric oxide production
Increased dependence of renal prostaglandins to maintain perfusion
Decreased vitamin D activation
Impaired secretion of acid load

[a] GFR, glomerular filtration rate; ADH, antidiuretic hormone.

Table 3.17 Morphological changes in kidneys with ageing.

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

Table 3.18 Functional changes in aged kidneys.

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

Table 3.19 Anatomical changes of endocrine glands with ageing.

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

Table 3.20 Age-related changes in the degradation of hormones[a].

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

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

in the submucosa and in the myentenic plexuses are key to the functional changes observed with ageing.[30]

The ageing kidney

The ageing kidney maintains its ability to regulate body fluid homeostasis under general conditions (Table 3.16). It becomes progressively limited in its ability to respond to stresses. These changes result from anatomic changes and also from alterations in tubular cell function and responsiveness to hormonal and haemodynamic factors.

The loss of renal mass is mainly due to progressive atrophy of the renal cortex, with relative sparing of the medulla. By age 80 years, between 10 and 30% of the glomeruli are completely sclerosed. The glomeruli of the outer cortex are affected the most (Table 3.17). There are also functional changes in aged kidneys. Renal blood flow decreases by ~10% per decade after a peak in young adulthood, and the renal plasma flow is reduced by 50%.

The cause of age-related changes in the kidney remain unknown.[31] One hypothesis, the hyperfiltration theory due to reduced nephron mass, proposes that a kidney with reduced number of glomeruli, has increased capillary blood flow through each glomerular bed and a corresponding high intracapillary pressure. This high pressure results in local endothelial damage, platelet aggregation and thrombin production, which leads to the release of growth factors from platelets such as (1) platelet-derived growth factor, (2) epidermal growth factor, (3) fibroblast growth factor and (4) tumour necrosis factor alpha (TNF-α). These factors increase fibroblast collagen production and mesangial cell sclerosis. Angiotensin II secretion is then increased due to the disruption of vascular haemodynamics. As glomeruli become sclerosed, the amount of blood flow to each remaining nephron increases, further potentiating the damage. Oxidative stress and telomere shortening are thought to play a role in vascular damage. These changes result in an increase in the filtration function (glomerular filtration rate/renal plasma flow) with ageing.[32]

Functional and morphological changes occur in the aged that affect homeostasis are summarized in Table 3.18.

The ageing of the endocrine system

Ageing is associated with hormonal changes, and with anatomical changes of the endocrine glands as a result of programmed cell death, autoimmune destruction of the gland or neoplastic transformation of glandular tissue. Age-related changes could also occur in hormonal secretion secondary to physiological changes due to circadian and seasonal rhythm or in frequency or height of hormonal pulses. Other changes with ageing include (1) altered bioactivity of hormones, (2) altered transport of hormones to binding receptor sites, (3) altered hormone–receptor interactions or (4) postreceptor changes. Ageing is associated with alterations in plasma membrane properties, intrinsic changes in cellular enzyme activity and changes in calcium mobilization and gene expression. Ageing is associated with important structural changes (Table 3.19).

Changes in hormone secretion are noted with ageing. They are related to altered endocrine cell physiology rather than cellular depletion. Age-related changes in the pituitary

Table 3.21 Changes of organ systems with ageing.

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

gland are attributed to altered pulsatile pattern of hormone secretion. Desynchronization of various biological rhythms occurs with ageing. Glandular sensitivity to secretagogues is also affected, with some glands having reduced, increased, inhibited or no alteration in response. Finally, clearance of hormones is also altered with ageing. For many hormones, peak function occurs between 20 and 30 years of age and then declines at a constant rate thereafter.

Changes occur in the aged endocrine glands that affect homeostasis greatly (Table 3.20). A decrease in insulin growth factor I receptor is associated with longevity in females. Increased plasma TSH is associated with longevity, which appears to be associated with an alteration in the TSH receptor.[33]

Ageing of other systems

A multitude of changes occur in other systems of the body (Table 3.21). The dysregulation of these systems affect homeostasis in a multitude of ways.

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

Key points

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

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CHAPTER 4

Psychological aspects of ageing

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Introduction

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

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

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

Successful psychological ageing is dependent upon mental vitality. Mental vitality can be described as psychological or intellectual energy. That is, given life's choices, how does the ageing adult face the challenge? What is the individual's mental vigour to cope with changing biopsychosocial changes? What has been their history of adapting and coping throughout life? Studies have found that ill health is related to problems with cognition, learning and motivation, thus challenging the elder's ability to cope.[1,2] In addition, Chou *et al*.[3] found that mood can affect decision-making abilities in the elderly. A happy mood was related to increased risk-taking activities and, conversely, information processing and motivation were affected by the mood of the individual As Kermis[4] so aptly put it, ageing is the greatest challenge.

Mental vitality encompasses present life-style choices, but also one's history of choices. These choices include reducing stress, establishing rest and relaxation, challenging the mind, cultivating satisfying relationships and activities and avoiding known risk factors such as smoking, poor nutrition, weight problems and excessive alcohol consumption. Equally important are the attitudes and beliefs that the older adult has about ageing that reflects how successfully one ages. A mentally vigorous older adult with a positive attitude will be able to cope better with life's challenges and make informed choices. Although cognitive deficits have been extensively written about, it is the positive changes and adaptive abilities that may be more important in daily living skills. Likewise, Reichstadt *et al*.[5] studied the opinions of community-dwelling older adults (60–99 years of age) as to what contributes to successful ageing. Four themes emerged from their focus groups: (1) the importance of having a positive attitude and being adaptable; (2) having security and stability with regard to living situation, finance and support resources; (3) physical health and wellness, but with mixed opinions on whether this is necessary; and (4) a sense of engagement and stimulation, defined as finding meaning in life, being useful with continued involvement in stimulating activities.

Life stage perspective

Here, the focus will be on the emphasis of mental vitality as a life stage approach. This developmental-stage theory emphasizes integration of life experiences. The developmental theorists attempt to describe human development as a sequence of stages or steps. Developmental-stage models

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hold that changes in the adult personality are results of interaction of the social and biological environment. How the individual interacts with others and integrates that interaction into his/her personality is determined by the developmental tasks that the person performs. These tasks are markers of the individual's movement through the life cycle. Each task combines some aspects of the person's biological, psychological and social functioning. Developmental tasks combine the drive towards growth of the person with the demands, constraints and opportunities of the social environment. These tasks occur for all people in approximately the same sequence, which may overlap each other without a particular onset or termination. Failure and delay in resolving these tasks may affect how successful one will be in resolving future tasks, adjustment and overall mental health. All of these tasks act to move the individual towards optimal psychological function and personal integrity if they are successfully accomplished. Similarly, Atchley[6] proposed the continuity theory of normal ageing, which observes that older adults use strategies reflective of their past experiences and views of self and their world. Change is linked to past perceptions and existing internal structures. Erikson,[7] the most familiar of the developmental-stage theorists, applied his approach to the aged. In his eight stages of development, the person has a conflict with two possible outcomes, adaptive or maladaptive solutions. If an early stage is resolved with a low degree of adaptation, resolving later stages will be more difficult. Erikson's last two stages directly apply to adults and ageing adults. These two stages are broad and cover many years, resulting in other theorists defining more definitive age-specific conflicts.

Havighurst and Peck postulated theories that have particular significance for the elderly; both authors elaborated on Erikson's psychosocial tasks with consideration of tasks of the older adult.[1,7–9] Havighurst[1] described the six tasks of old age as follows:

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

Ageing adults experience a variety of physical, social and psychological losses. These losses can affect mobility both physically and socially, resulting in increasing isolation. There is a chance that the environment will continue to diminish unless the individual takes action. Havighurst's focus was on reorganizing functions and expectations.[1] For example, older adults who do not accept their changing physical and health limitations and adapt may become maladjusted. Partner roles may change if one partner becomes ill. The partner who nurtured may need nurturing care; the healthy partner may have to assume new roles of banker, handyman and decision-maker. Old age is a time of almost constant change. Older adults who do not adapt or adjust flexibly may find themselves increasingly stressed and maladjusted. According to Havighurst,[1] the continued refining roles and expectations to meet environmental demands accomplish the maintenance of identity.

Peck's tasks[9] are summarized into three areas of conflict. The first is ego differentiation versus work–role preoccupation and finding a way to identify and appreciate self without the job or one's career as the marker of success. This includes satisfaction with retirement and children leaving home. The task is to find new ways, activities and passions to define one's self. The second is body transcendence versus body preoccupation, which is understanding the changes in the body and illnesses without being preoccupied with symptoms or illness concerns. The question is, can one live successfully despite age-related changes and disease states? Many older adults cope with illness and live successful lives despite pain or infirmity. Others are preoccupied with their illness, by constantly talking about their symptoms, medication requests and frequent doctor appointments or 'shopping'. Lastly, the third area of conflict is ego transcendence versus ego preoccupation. This process is the coming to terms with the reality of death, putting closure on the past, ensuring the welfare of children and others and leaving a legacy. There is a need to share one's wisdom, knowledge and experience. Conversely, if maladaptive, there is a tendency to treat the world as if it will end with their death. This person may not make wills or plans for the future or for anything that would go on after their death.[9]

In summary, the personality is constantly changing in response to the individual's adaptation throughout life. Life challenges can occur at any time in the life cycle, but older people are more likely to have to confront more challenges simultaneously. Losses, physical and functional changes and cultural expectations stress older adults when their psychological reserves are low and their social supports are diminishing.[4]

What do we know?

In 2011, the first wave of 'baby boomers' (65–74 years old) will be retiring. For the next 20 years, 74 million baby boomers will retire. The 74–95-year-old cohort will steadily increase their numbers and also their life expectancy. As a group, the frail elderly is growing the fastest. In the United States, the 85+ age group will triple to 19 million by 2050.[10] Worldwide, the World Health Organization (WHO) estimates there are 4 million elders over the age of 85 years. Further, since 2007, the global population of all ages of older people has increased to 506 million worldwide.[10,11]

Ageing is not uniform or static. There is differentiation among the ageing, commonly divided into four groupings of the young-old (60–70 years of age), the old (71–74 years of age), the old-old (75–84 years of age) and the frail-old (85 years of age and over).[12–14] Each grouping has different tasks, abilities and issues. For example, the 60–70-year-old groups may still be employed and be more active. They may be dealing with retirement, considering housing options, developing leisure activities and relationship issues.

The 71–74-year-old group may be adjusting to retirement, loss or changes in work–role identity, income changes, friends moving or ill, widowhood and readjusting time management. Neugarten[13,15] noted that chronic illness and role losses were more characteristic of those over the age of 75 years. She further contended that the 55–74-year-olds are similar to the middle-aged who have fairly good health and are as active as they wish.

Riley and Suzman[14] further divided the old-old into the old-old and the frail-old. The old-old group may have more medical conditions, take more medications and may require more support services by either family or agencies or both. There are more losses, more issues with dependency and those related to assisted living situations. For couples, one partner may need more care and placement, resulting in the couple being separated.

This group is primarily female, widowed and more likely to face declining functional ability without a spousal caregiver. The old-old and particularly the frail-old group experience more physiological changes, more comorbid medical conditions, more frailties, higher rates of dementia and loss of connectedness. Connectedness is the desire to feel connected to others, their homes and community. This sense of connectedness is threatened when there are limitations in functioning, necessitating moves to a more secure and assisted living environment, removing the elder form the security of their neighbourhood and their home.[16]

Overall, the frail elder is more likely to be in a supported living setting with more health problems, is more dependent upon others to meet their daily needs and generally takes longer to recover from acute illnesses.[17,18] Many of this population, primarily women, may outlive their financial and health care resources.[18,19] With advancing age they are more likely to live in poverty, have increased risks for health and social problems. There is a corresponding demand for supportive services, long-term care solutions and more money allocated for health care and services.

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

Age-related psychological changes

Intelligence

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

IQ increases until the 20s, then levels off and generally remains stable throughout the life cycle. With ageing, there is decreased speed in timed tests. Poor health represents an adverse factor in the older adult's performance. If given more time, the older adult is as accurate as a younger adult is. In general, older adults perform better in everyday practical tasks over laboratory-based tests. Performance on the Wechler Adult Intelligence Scale (WAIS) demonstrates that older adults have an increase in verbal skills, while there is a decrease in tests of performance. Results show that intelligence is stable until the 70s, when there is a decrease in performance countered by an increase in verbal skills.[2] These verbal skills reflect the knowledge and skills acquired over a lifetime.

Ageing influences intellectual functioning. Changes in motor skills and slower decision-making time affect reaction time. Performance is also affected by changes in cerebral cortex functioning and cardiovascular deterioration. When decision-making, older adults have been found to sacrifice speed for accuracy and to reject quick, simplistic solutions to problems, preferring to work slowly and to examine issues from a variety of perspectives before responding. Older persons are more likely to make errors of omission rather than errors of commission, which suggests cautiousness, deliberateness and anxiety.[20] As a compensatory strategy and to avoid embarrassment, many older persons avoid unfamiliar activities and places. This cautiousness may be mistaken for resistance or obstreperousness. In addition, mood and beliefs about ageing affect one's response to testing and evaluation.[3,21,22]

A word of caution is advised, many older adults do not have the advantage of many years of formal education as compared with younger persons and have been years away from the classroom environment.[2] Deliberateness, slower response time and time away from traditional school activities impact tests of intellectual abilities.

Clinicians need to evaluate clearly the impact of physical infirmities, compensatory skills and the older adult's social environment before coming to any conclusions regarding intellectual decline. The impact of the living situation,

lack of stimulation and isolation may constrain intellectual functioning and should not be ignored.[2] If healthy and fit, the older adult's response time is no different from that of less healthy younger people.

Memory

The capacity to learn continues throughout life. Optimal learning involves reading or following instructions on how to organize information, finding tasks meaningful and rewarding and being able to link visual memory with auditory information. There are three phases of information processing – encoding, storage and retrieval. With ageing, more time and effort are required to encode information. Sensory changes can reduce memory efficiency. Because sensory memory lasts less than 10 seconds and with ageing sensory changes, the older adult is less able to encode as well. Short-term memory lasts a few seconds and declines with age.

Recall involves search and retrieval of information from storage. Recognition requires matching information in storage with information obtained in the environment. Recognition abilities remain stable over time.[20] All ages do well in recognition tasks, but recall diminishes over time. It is easier for older adults to do tasks of recognition than recall information.

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

As important is the impact on one's belief that memory loss is inevitable. Lineweaver *et al*.[21] found that these beliefs are pervasive and stereotypical in that study participants rated individuals with positive personality traits as having better memory and less decline than those adults with negative personality traits. For clinicians, a more thorough assessment may be indicated of the older adult's beliefs that may influence their performance in cognitive tasks.

Many older adults adapt fairly well and deficits may not be evident until a traumatic event occurs or is uncovered by a skilled clinician. Using compensatory strategies to augment memory, such as use of calendars and notes, taking time and practicing new material, is indicated. Structure and familiarity also help in improving memory and retention. With slowed recall and physical decline, there is a slower response, which can be misconstrued as more significant memory deficits or resistance.

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

Sensory

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

Creativity

Even though creativity is generally not considered a component of psychological functioning, it is an area that is a part of mental vitality and quality of life. There have been many debates about whether creativity is limited to a few and that it declines with age.[23] Research shows that creative thinking is a universal ability that helps adults manage satisfying lives. Creativity is a complex of traits, skills and capacities, including the ability to work independently, curiosity, unconventional thinking, openness to experience and tolerance of ambiguity.[23,24] Cognitive psychologists define creativity as a mental process like imagination and intuition. The newer definition is particularly relevant to the older adult. It is the integration of cognitive processes, knowledge, thinking style, personality, motivation and environment over a lifetime. Creativity is a way to address and resolve dissatisfactions and improve quality of life and can be a response to limits and an uncertain future.[23,24] Older adults appear to experience a decrease in divergent thinking, the ability to generate novel ideas, but this is a qualitative change in the creative process. In contrast, there is an increase in crystallized intelligence and integrative or convergent thinking.[25] Later life may afford more time for reflection, life review and creative pursuits aimed at the development of one's life story and the filling in of gaps and discontinuities. This creative process, which is similar to Butler's life review,[26] is a positive therapeutic process. Adams-Price[23] concluded that late-life creativity reflects aspects of late-life thinking: synthesis, reflection and wisdom.

Implications for practice

Ageing is an adaptive challenge. Mental vitality is the vigour needed to meet this task. As clinicians, continual

evaluation of the older person's understanding of the implication of age-related changes and losses is required. Identifying coping skills and adaptive strategies is also paramount an effective relationship and treatment planning. To incorporate the aforementioned psychological changes into practice, the recommendations are made:

1 Face-to-face education should occur, presenting the information in small increments and supplemented with one-page practical handouts to carry home.

2 Helpful teaching techniques include teaching time, with practice and episodic spot checks to reinforce or to correct, and a telephone phone number and contact person to call if they have questions or concerns.

3 Allow time to complete forms in a setting conducive to writing.

4 Printed materials need to be in larger, boldface type and simplified to adjust for sensory changes. The guidelines of the Americans with Disabilities Act recommend that print be at least 18-point font. Signs should be in large print or symbols with contrasting background of eggshell, matte or non-glare paper for easier reading and to clarify directions.[27]

5 Observe accessibility and visibility issues in the physical environment. Are the directions and locations easy to follow? Lighting should be 100–300 lux to ensure adequate vision and easy reading.[27]

6 Encourage the older person to take notes or write their concerns before their appointment.

7 If necessary or beneficial, suggest that the older person bring someone to assist or take notes.

8 Encourage the older adult's participation in the treatment planning.

9 Allow the older person the opportunity to present concerns, fears or objections to the plan.

10 Allow them time to process information and study their options.

11 Ask how they are coping and what coping strategies they use. For example, 'How do you handle this?', 'You have a lot to deal with', 'How are you holding up?' or 'What helps you?',

12 Encourage innovative or creative solutions. Ask how they would solve a problem.

13 Referral to support group, if it exists, for their medical condition.

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

Conclusion

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

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

Key points

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

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CHAPTER 5

Ageing of the brain

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Even compared with the closest animal species (great apes), the human species is characterized by an exceptionally high brain/body weight ratio and a long lifespan. In this chapter, it is obviously impossible to cover the immense field of both the physiological and evolutionistic features of human brain ageing and the major pathologies that affect, at an increasing rate with age, elderly people. A number of detailed reviews on these issues can easily be found. Here we report some recent research lines that seem relevant for understanding better the 'physiology' of brain ageing and the pathophysiology of major diseases affecting cognition such as Alzheimer's disease, and we review the input of recent brain imaging methods to explore clinically brain function and tissue changes in the elderly.

Increasing human longevity has been a constant trend worldwide over past decades. Improvement of socioeconomic conditions and nutritional resources, together with the prevention and treatment of major pathologies such as infectious, metabolic, vascular and heart diseases, have contributed to a longevity increase from ~60 to ~80 years during the twentieth century in Western countries. Estimations of the prevalence of clinically diagnosed dementia in nonagerians ranges from 20 to 30%, with a higher risk in women;[1] therefore, as age is one of the major risk factors for Alzheimer's disease (AD) and the frequency of vascular lesions also increases with age, one may wonder whether, in the extreme elderly range, a disease-free brain should be regarded as a (desirable) norm or whether it is observed in only a minority of cases.

Is there physiological ageing for the brain?

From an evolutionist point of view, a compelling question is what is the advantage for our species to have a prolonged, senescent period of life in which women cease to be reproductive? Notwithstanding culture-based influences that provide senior members of a group with a protected and honoured social status, it has been proposed that elderly individuals, especially grandmothers, could play a specific role in the transmission of knowledge concerning foraging and other context-dependent hints and strategies crucial to individual and social survival. Therefore, it is conceivable, on biological grounds, that non-reproductive, ageing individuals who can communicate, over a significant period, their experience to junior congeners and participate in the (prolonged) education of children represent an evolutionarily advantage.[2] From a physiological perspective, it should be remarked that the maintenance of the large and complex human brain supporting efficient, long-lived episodic memory implies especially high energy consumption as the brain's energetic needs relative to the total body metabolism is remarkably high in humans (~20% of the body energy consumption). The intimate basis of this enormous energy need probably relates to (i) the considerable membrane surface of most neurons whose dendritic and axonal arborescence extend very far from the cell body and (ii) the energetic cost of molecular trafficking and ionic exchanges throughout membranes of the 'neural tree'. It should be noted that some regions of the consciousness-related 'default mode' network, such as the posterior cingulate cortex, also support high-level autonoetic memory representations. It might not be pure coincidence that this region is also characterized by both a tight coupling between oxidative energy consumption and synaptic firing[3] and heavy binding of amyloid-specific ligands at early stages of AD.[4,5] Further, the effect of constant learning and maintenance of long-term memory during ageing have to relate also to morphological plasticity in the brain. A very slight, non-linear and brain-wide trend to grey matter thinning with preponderance in the parietal and frontal convexity is observed in normal subjects from the second to the eighth decade; this slight frontal atrophy is associated with a decrease in performance on executive and working memory tests.[6] By contrast, the evolution of white matter volume proceeds differently over decades, with a slight growth trend from the third to the sixth decade followed by a rapid decline with further ageing;[7]

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white matter abnormalities in magnetic resonance imaging (MRI), typically small hyperintensities in the periventricular regions, increase with age and represent an independent risk factor for dementia and stroke.[8]

At the microscopic level, the estimation of the reduction in the density of neurons in the cortex has led to controversies; differences between cortical territories might account for these discrepancies, but some moderate, age-related decrease in branching in the dendritic tree and the size of neurons has been more consensually acknowledged (for a review, see Burke and Barnes[9]). Interestingly, normal ageing seems to relate to a shrinkage of cortical mini-columns,[10] although adaptive plasticity may also lead to longer terminal segments dendritic trees[11] in addition to new synapses and neo-neurogenesis[12] that might offset the effects of disappeared connections. At the molecular level, neural plasticity depends on a variety of mechanisms, among which one should note the role of immediate early genes (*CJun, Cfos* and *Zif238*), in addition to a number of other pathways involved in axonal growth, cytoskeletal assembly/transport, signalling and lipogenic/uptake pathways, according to Rowe *et al*.,[13] who also described upregulation in immune/inflammatory, lysosomal, lipid/protein degradation, cholesterol transport, transforming growth factor and cAMP signalling pathways. The influence of education and sustained, challenging cognitive activities on brain structure and functions has been described as the 'cognitive reserve hypothesis' by Stern *et al*.;[14] such an influence of cognition-related neural activities over the lifespan would also elicit brain resilience to pathology. Although the existence of learning-related brain plasticity (from cellular to gyral morphology levels) is beyond dispute,[15] these effects across subject groups differing in education have not been unequivocally confirmed and the protective mechanisms of 'cognitive reserve' against brain pathologies are still poorly understood.

Pathological ageing: proposed cellular and molecular mechanisms

The challenging need for maintenance over decades of high energy consumption in the hugely complex cellular brain architecture has been mentioned above; in the context of such human-specific physiological condition, a number of mechanisms that would be at the origin of ageing-related degenerative diseases have been put forward, especially a lack of clearance of toxic metabolic by-products, oxidative stress and disturbed Ca^{2+} homeostasis. A number of neurodegenerative diseases are associated with the aggregation of misfolded constitutive cellular proteins such as tau, α-synuclein and β-amyloid.[16] The last protein has attracted considerable attention as a consequence of its major implication in the most frequent, age-related degenerative brain disease, AD.

The specific role of the β-amyloid protein in its various monomeric, oligomeric and aggregated or fibrillary forms in the pathophysiology of AD remains to be elucidated, in addition to the mechanistic link between β-amyloid accumulation and pathological accumulation of the hyperphosphorylated form of tau protein in neuronal microtubules. The aggregated, mature form of β-amyloid constitutes the core of senile plaques observed in the brain of AD patients and also in normal elderly subjects, although to a far lesser extent; this typical neuropathological feature probably represents the final state of the pathology process rather than the origin of neuronal death in AD. Oligomeric, soluble β-amyloid has been shown to have toxic effect at the synaptic level via overstabilization of mGlu5 receptors provoking excessive intracellular calcium influx;[17] damage to synapses seems to be one of the earliest lesion stages in pathological ageing with synaptic loss located in key regions such as the mesial temporal cortex.[18] The chronic activation of pro-inflammatory pathways eliciting glial cell activation has been outlined as one of the likely basic mechanisms leading to cell death in neurodegenerative diseases, and even β-amyloid has been related to such inflammatory pathways, putatively activated to fight microbial diseases.[19] One of the only established important genetic risk factors in the late-onset forms of AD is genotype epsilon4/epsilon4 of the ApoE protein, while ApoE3 has protective influence for cardiovascular diseases in ageing. In evolutionistic terms, ApoE4 would be an old form whereas ApoE3 seems to have been selected later, perhaps as a consequence of the changes in the human diet when it went on to involve more and more animal fat. ApoE has a major role in the transport of cholesterol and elevated values of cholesterol blood concentration also represent a risk for AD. A direct binding mechanism has recently been suggested between cholesterol and the C-terminal portion of the amyloid precursor protein.[20]

At the intracellular level, the key role of Ca^{2+} in a number of metabolic processes, from energy production to gene regulation, consists in a transient influx of calcium in the cell, quickly buffered by specific protein transporters and by sequestration in organelles such as mitochondria. Mitochondria play a key role in intracellular energy supply, especially in the neuron synapse regions, and are affected by ageing with changes in their structure and decay of their efficiency, leading to oxidative stress with increase in the cellular concentration of oxygen reactive species (for a review, see Toescu and Verkhratsky[21]). Age-dependent decay of the ionic exchange systems that normally induce rapid calcium elimination from the cytosol relates to various pathogenic pathways that may lead to apoptosis. The various biochemical mechanisms by which excessive calcium concentrations can be alleviated are good examples of the compensatory pathways that can take place in some cell populations to resist pathological ageing. However, it

seems that specific neuron types are more exposed to the toxic effects of increased intracellular calcium concentration or the regulatory mechanisms elicited by this trend. For instance, hippocampal pyramidal cells are characterized by a decrease in the number of NMDA receptors with ageing; this effect may be a way to diminish toxic Ca^{2+} influx but also has the important consequence of a reduced efficiency of memory processes.[22]

Brain tissue depends vitally on a constant supply of oxygen and glucose by blood vessels. Ageing induces a progressive thickening and stiffening of arteries that alter the haemodynamics of cerebral vasculature and the efficiency of the transfer of energy metabolites to glial and neural cells. Hypertension and diabetes are major causes of such changes in the structure of blood vessels.[23] The clinical significance of such vascular changes has already been emphasized above, concerning brain white matter and the periventricular lesions (hyperintensities in MRI) that are observed to increase with age, as a consequence of pathological changes in the small artery system in these deep brain regions (for a review, see Moorhouse and Rockwood[24]). In cohorts of very old patients, neuropathological findings have demonstrated an increasing prevalence of cerebrovascular lesions as a conjoint pathology of typical AD lesions.[25]

Changes in large neuroendocrine systems and in general behaviour during ageing

Although not part of mainstream research, the influence of ageing on the whole neuroendocrine system is compelling. The most obvious example is the fall of ovarian estrogen production at menopause; estrogens, in addition to the cyclic interaction with its hypothalamic control pathways, are known to be involved in the control of mood, memory and cognitive and general behaviour.[26] Akin to this pathway is the stress control system, mainly represented at the hypothalamic level by the corticotropin-releasing hormone (CRH) secreted by the paraventricular nucleus; this system, which undergoes inhibitory control from the hippocampus, is upregulated in depression and to a lesser extent in AD. The implication of the stress system in general behaviour is also compelling when considering that vasopressin secretion co-localizes with that of RCH. Vasopressin is also secreted in a rhythmic way by the supra-chiasmatic nucleus, which is viewed as the biological clock of the brain and is responsible for the circadian changes in the stress system.[27] Ageing affects these neuroendocrine systems and the latter are involved in the major circadian behavioural changes, namely the sleep–wake rhythm (for a review, see Buckley and Schatzberg[28]). Sleep and wake alternations, which result from global brain functioning, underlie consciousness and have major influence on cognitive performance, especially episodic long-term memory (LTM). Non-rapid eye movement sleep (or slow-wave sleep) and the density of spindles in sleep stage 2 have been associated with efficient consolidation of LTM contents;[29] nevertheless, these effects seem specific to episodic memory and rapid eye movement (REM) sleep would also contribute to them in terms of contextual enrichment;[30] consolidation may be supported by the transfer of memory contents from the hippocampal formation to the prefrontal cortex. Age-related changes in sleep consist of a shortening of the successive sleep stages (especially the deepest stage 4), giving rise to an instability of the sleep structure, frequent nocturnal wakening and earliness of morning wakening. The EEG shows that typical events such as delta waves and K complex are less frequent and reduced in amplitude. Decreased performance of episodic memory in elderly healthy subjects relative to young control subjects might be related to the impoverishment of slow-wave sleep in the former. AD affects deeply sleep behaviour including increasing phases of diurnal somnolence and agitation at sunset. Damage to the cholinergic system which is caused by AD is strongly associated with shortened and impaired REM sleep (for a review, see Gagnon *et al*.[31]).

Assessing age-related physiological and pathological changes in brain anatomy and function: the input of brain imaging

Changes in cerebral blood flow and metabolism

Soon after the initial description by David Ingvar of the 'hyperfrontal' pattern of cerebral blood flow (CBF) in resting wakefulness,[32] the effects of age on the so-called 'hyperfrontality' have been reported. Studies agreed on the progressive disappearance of hyperfrontality during the fifth and sixth decades[33,34] and these observations were the first to point to the prominent susceptibility of the frontal cortex to healthy ageing. Since then, numerous metabolic studies using [^{18}F]fluorodeoxyglucose positron emission tomography (^{18}FDG PET) imaging have confirmed the earlier and higher functional vulnerability of the frontal cortex with ageing that may be worth distinguishing from the relative sparing of the mesial temporal and hippocampal cortices, which, opposingly, are early affected by AD.[35] However, other studies have found that, after correction of the ^{18}FDG uptake values for partial volume effects, no cortical region exhibited a significant correlation with age (although moderate, non-significant correlations can still be observed in particular in the frontal cortex), whereas measures of white matter integrity correlated with global and regional cerebral glucose uptake, indicating that white matter degradation may contribute

significantly to the functional changes observed in brain normal ageing.[36] However, a recent study by Chen *et al*.,[37] using arterial spin labelling for measuring cerebral blood flow, showed that the observed age-associated reductions were independent of regional atrophy evaluated by cortical thickness and, very interestingly, that the spatial distribution of CBF decreases spans the regions of the default-mode network.

Changes in brain macrostructure and microstructure

Progress in MRI techniques now allows sensitive and robust measurements of macrostructural and microstructural changes in brain grey and white matters that, combined in a multimodal approach, are substantially improving our knowledge of the impact of normal and pathological (mainly neurodegenerative) ageing on brain structure. These techniques provide, with high spatial resolution, anatomical (macrostructural) information (voxel-based mophometry, cortical thickness) and microstructural information (fractional anisotropy, mean diffusivity, diffusion decay imaging and tractography using diffusion MRI, T1 intensity and T2* relaxation rate for myelination and iron content imaging), each of these measures shedding light on different aspects of the healthy ageing or degenerative processes affecting our brain.

A longitudinal study by Fjell *et al*.[38] showed that the cortical atrophy consecutive to an ageing period as short as 1 year can be readily measured by changes in cortical thickness and volume using MRI. The annual atrophy rate varied across the cortex and was about 0.5% per year on average in a group of healthy subjects aged 60–91 years, the highest annual rate being measured in the hippocampus (–0.84%). Comparatively, the annual atrophy rate was increased in AD patients, with 1% per year change or more, reaching 2.5% in the posterior cingulate/precuneus region and lateral temporal cortex.

Numerous studies using the voxel-based morphometry approach also reported increased cortical atrophy with age, changes often predominating in the frontal cortex.[39] The same authors also reported changes in volume with age in the white matter (WM), especially in the anterior thalamic radiation, the anterior limb of internal capsule and the cerebral peduncle. They also found a negative correlation of fractional anisotropy (FA) with age in most of the WM regions, due to decreased radial anisotropy, and observed a positive correlation between age and mean diffusivity in most of the WM regions, with a relative sparing of the occipital lobes.

Combining cortical thickness, T1-weighted signal intensity and T2* relaxometry in a multimodal study aiming at differentiating maturational from ageing-related changes in the cerebral cortex, Westlye *et al*.[40] demonstrated a non-monotonic relationship of T1-weighted signal intensity with age, with an increase during the maturational phase (up to 30 years), followed by a plateau during middle age and a decrease in senescence that contrasted with the quasi-linear decrease in cortical thickness. They observed that the pattern of maturational development and age-related decline of the signal intensity measures were in agreement with the notion of a posterior–anterior gradient of cerebral maturation but at odds with the early frontal vulnerability reported in metabolic or morphometry studies. Indeed, while the frontal areas were the latest to mature fully as indexed by T1 signal intensity, they were not among the first to decline with advancing age according to this parameter. The authors stressed their observation that cortical grey matter signal intensity alterations were largely independent of concurrent cortical thinning and iron accumulation and possibly reflected alterations in myelination processes and synaptic density.

In addition to the cortex, subcortical nuclei are also affected by age and the corresponding changes can be evidenced by advanced imaging techniques. Measuring atrophy, iron deposition mean diffusivity and fractional anisotropy in seven subcortical structures, Cherubini *et al*.[41] showed that the T2* relaxation time in the putamen combined with the volume and the mean diffusivity of the thalamus accounted for more than 70% of the age variance in a group of 100 healthy subjects aged 20–70 years.

The advanced MRI techniques that contributed to improving our knowledge on the brain correlates of physiological ageing, as exemplified by the studies cited above, have also been applied to the study of the pathological processes that affect the ageing brain, in particular to the main two neurodegenerative diseases where age appears as a major risk factor : Alzheimer's disease (AD) and Parkinson's disease (PD). Cortical thickness in particular has been shown to help in the early diagnosis of AD. For example, using a normalized thickness index, Querbes *et al*.[42] were able to predict correctly, at the individual level, the evolution (or non-evolution) to AD for 76% of subjects with amnestic mild cognitive impairment, as early as 2 years before conversion. The interest in the anatomical measure for AD early diagnosis mainly follows from its immunity against the cognitive reserve which may mask the cognitive decline for many years in highly educated subjects. As another example of the potential of multimodal MRI in the diagnosis of neurodegenerative diseases, Péran *et al*.[43] demonstrated the nigrostriatal signature of PD by combining iron deposition and diffusion measures in the substantia nigra and the putamen. These imaging markers alone provided a 95%, cross-validated global accuracy in discriminating PD patients from controls. This work opens up interesting perspectives for monitoring disease progression and long-term drug impact.

Changes in brain intrinsic connectivity

The study of functional communication between brain regions at rest using MRI, the so-called resting state functional connectivity MRI (rs-fcMRI), has attracted attention in the past few years (for a review, see van den Heuvel and Hulshoff Pol[44]). In particular, one of the networks supporting brain intrinsic connectivity, the default-mode network (DMN),[45] has been shown to be affected by normal ageing and AD. Smaller and slower task-induced deactivation of the DMN has been observed in older healthy subjects[46] and these deactivations were even more reduced in AD patients.[47] Sambataro *et al*.[48] confirmed previously reported results observed in healthy ageing and showed that age-related alterations of the DMN, in particular in the connection between the posterior cingulate (PCC) and the prefrontal cortex (PFC), correlated with the decline in working memory of older subjects. These observations, in line with those of Andrews-Hanna *et al*.[49] on the correlation between decreased PCC–PFC connectivity and decline in executive functions and memory in older adults, may reflect, as suggested by Sambataro *et al*., a deficit in cognitive control and resource allocation possibly related to a decrease in dopaminergic innervation of the PFC in ageing. Interestingly, the intrinsic connectivity between the PCC and the hippocampus has also been shown to predict the performance on an associative memory task in cognitively intact elderly subjects.[50]

The results of the studies cited above suggest that impaired intrinsic connectivity may serve as an imaging biomarker for the early diagnosis of AD. In this perspective, a recent study by Yao *et al*.[51] reported very interesting results. Using a global, graph theoretical approach, they showed that the cortical networks of normal controls, MCI subjects and AD patients all exhibited small-world properties, but that abnormal nodal centrality was detected in MCI and AD, in addition to significant changes in inter-regional correlations. Their findings indicate that a loss of small-world characteristics can be shown early in the progression of disease, the MCI subjects displaying an intermediate pattern between those of controls and AD patients.

Key points

- Grey matter thins slightly with ageing, particularly in the frontal cortex, and this is correlated with the decline in executive function.
- Impoverishment of slow-wave sleep may lead to decreased performance in episodic memory.
- Blood flow decreases with ageing, especially to the frontal cortex.
- Cortical atrophy with a predominance in the frontal cortex occurs with ageing.

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CHAPTER 6

Epidemiology of ageing and disability

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Ageing and chronic disease epidemiology

According to the United Nations Department of Economic and Social Affairs' 2002 report, *World Population Ageing: 1950–2050*,[1] the number of older adults has tripled in the last 50 years and is expected to again triple over the next 60 years. This unprecedented population shift is a consequence of steep declines in both fertility and mortality. The percentage of the population aged 60 years and over will equal that of individuals younger than 15 years by 2050 because of the projected decline in birth rates. This population shift is profound. In some developed countries, older persons already far outnumber children. Although the rate of these changes and subgroup proportions vary by region of the world, all regions are experiencing increasing longevity (Figure 6.1). The most rapidly growing group world-wide is those 80 years of age and over. The speed of the demographic transformations is unprecedented. For example, this seminal report[1] has revealed that 66% of the global increase in the world occurred in less developed areas over the last half century. The result of these demographic changes will culminate in four-fifths of the world's older population living in the less developed regions of the world.

In the United States, population projections indicate that one in five people will be aged 65 years or over by 2030.[2] According to these figures, between 2025 and 2030 the population aged over 60 years will be growing 3.5 times more rapidly than the total population. According to figures from the National Service Framework for Older People[3] in England, the number of people over 65 years old has more than doubled since the early 1930s, resulting in one-fifth of the population in England being comprised of persons over 60 years of age. Also, between 1995 and 2025, it is projected that the number of people over the age of 80 years will increase by 50% and the number of people aged over 90 years will double.

The public health significance of these demographic transformations includes the increased burden of chronic disease and disability on health care and socioeconomic impacts on care giving. The focus of health care must be related to reductions in age-specific disability and comorbidities. Current data based on the United States Vital Statistics show that heart disease and cancer are the top two leading causes of death for whites, blacks, American Indians/Alaska Natives, Asian/Pacific Islanders and Hispanics.[4] This is followed by chronic lower respiratory disease, stroke, diabetes, influenza and pneumonia (Table 6.1). However, these rates vary by racial and ethnic group. Life expectancy at the age of 65 years in 2006 was 17 years for men and 19.7 years for women, an increase of 1 and 0.7 years, respectively, since 2000. Diabetes is increasing in prevalence in older men and women. Men have a higher rate of both diagnosed and undiagnosed diabetes at 26% versus 24% for women. In addition, the rate of diabetes among those aged 65 years and over increased over three times faster among non-Hispanic black men. Although the prevalence of heart disease appears unchanged in the last decade, men continue to be diagnosed and suffer from heart attacks at a higher rate than women (Table 6.2). Non-Hispanic white males have the highest prevalence of diagnosed heart disease in the United States.

World Population Ageing: 1950–2050[1] describes the total dependency ratio as a measure of potential social support needs. Therefore, dependency can be used as a proxy for disability in older adults. Dependency ratios offer important information about the relative impact of ageing on the world's population. The ratio between the dependent population (both young and old persons requiring support) is projected to shift, with the older population constituting an almost equal component of dependency with the younger population and even to rise to 63% of the total dependency ratio in developed regions by 2050. The importance of these numbers is that health care needs to address risk factors of disability in the ageing to stem the burden of dependency.

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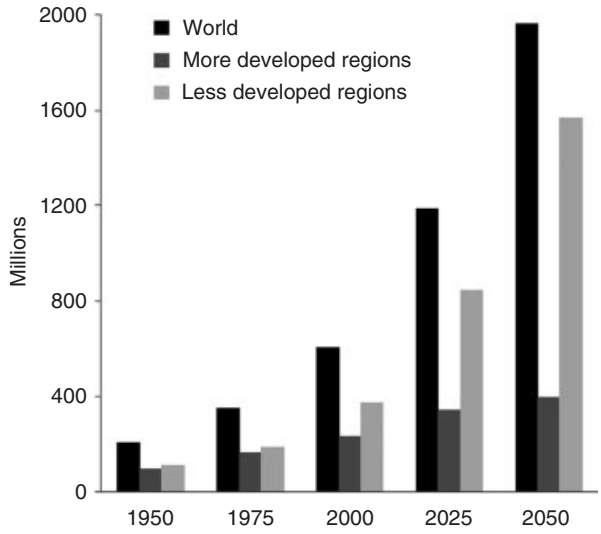

Figure 6.1 Expansion of the population aged 60 years and over: world and development regions, 1950–2050.[1]

Table 6.1 The leading causes of death in the United States in 2006.[41]

1	Heart disease: 631 636
2	Cancer: 559 888
3	Stroke (cerebrovascular diseases): 137 119
4	Chronic lower respiratory diseases: 124 583
5	Accidents (unintentional injuries): 121 599
6	Diabetes: 72 449
7	Alzheimer's disease: 72 432
8	Influenza and pneumonia: 56 326
9	Nephritis, nephrotic syndrome and nephrosis: 45 344
10	Septicaemia: 34 234

Table 6.2 European Union – Eurostat data: circulatory disease/cancer (two-thirds of deaths).

Circulatory diseases (heart attacks, strokes and other circulatory diseases)
41% of all deaths
42% of all deaths for 65–84-year-olds
Cancer
25% of all deaths
Highest cause of mortality for 45–64-year-olds

The response to population ageing needs to focus on the identification of risk factors and the development of effective prevention and treatments for disability. An additional focus is shortening the period of disability in the ageing population. As Hubert *et al*. noted,[5] the approach should be similar to reduction in cardiovascular incidence rates: risk factor models are identified from epidemiologic data and interventions are developed focusing on modifiable or reversible factors. Increased dependency equates to increased care taking and financial burden on families and increased institutionalization of older persons. Therefore, addressing the needs and interventions that accompany disability is rooted in targeted research. Longitudinal studies offer insight into associations of risk factors with disability.

The study of ageing and related diseases has been gradual and has occurred in response to changing population demographics. In the United States, the National Institutes of Health established one of its 27 Institutes and Centers as a National Institute of Ageing in 1974. This signalled interest and support for initiatives in ageing research.[6] In addition, many programs in gerontology and geriatrics were established. The consequence of these developments has been new studies pertaining to various aspects of ageing and geriatric research emerging as an important focus of interest. Population-based health studies around the world have taken initiatives to include older people in data collection and analysis. Prospective longitudinal studies will be important in advancing research and health services for chronic disease and disability that affects older persons. The ultimate goal of these activities is to increase disability-free years and improve quality of life. Therefore, a shift will be necessary to study not only mortality risks, but also risks and modifiable aspects of disability related to disease. Cooperative research that occurs through programs such as EU Public Health Programme and the Survey of Health, Ageing and Retirement in Europe (SHARE) are examples of important sources of data on ageing that can be used to advance aforementioned aims.

Epidemiological research is an important step in developing prevention strategies and creating recommendations and guidelines specific for older adults. In addition to epidemiologic knowledge, clinical studies and judgment along with patient preferences conjointly contribute to evidence-based medicine (see Figure 6.2).

Disability and ageing

Disability types

Because disability often complicates and accompanies ageing, it is an ever-present consideration affecting decision-making in geriatric medicine. Disability can be especially burdensome for women, those residing in poverty and minorities. The ability to distinguish the types or trajectory of disability is an important focus of health sciences research. These issues are also imperative for assessing the need for services and economic appropriation for health care services. Several studies have provided useful data on the prevalence, incidence and changes associated with disability.

Figure 6.2 Practical clinical applications influencing decision-making.

The type of disability most often associated with older persons is physical loss of function. Physical losses are usually measured by the ability to accomplish activities of daily living (ADLs), instrumental activities of daily living (IADLs) and functional limitations. According to the European Health Expectancy Monitoring Unit[7] (EHEMU) calculations from SHARE, women live over half of their projected life expectancy at the age of 65 years with one or two conditions or morbidities. The conditions or morbidities include heart disease, hypertension, high cholesterol, cerebrovascular disease/stroke, diabetes/elevated blood glucose, chronic lung disease, asthma, arthritis, cancer/malignant tumour, stomach/duodenal ulcer, peptic ulcer, Parkinson's disease, cataract and hip fracture. Although this list is long, it is notable for including five of the leading causes of death noted in Table 6.1. Also, these figures should be examined in the light of the longer life expectancy of women. According to the EHEMU's 2006 report,[7] women appear to experience poorer physical functional health than men and spend considerably less time, 27% compared with 45%, after 65 years of age without physical limitations. Also, 20% of expected years at age 65 years, for both men and women, are spent with severe limitations.

The US National Center for Health Statistics[8] analysed data from the 2001–2007 National Health Interview Survey (NHIS) conducted on a non-institutionalized United States population and noted an increasing incidence of age-associated physical limitation. In this sample of 238 018 people aged 50 years and over from the Sample Adult component of the NHIS, persons' physical limitations were assessed by eight separate questions reflecting difficulties with certain activities because of health problems. Individuals aged 80 years and older are 2.5 times more likely to have one or more limitations than individuals aged 50–59 years. Moreover, the percentage of United States adults with three or more physical limitations also increases from 8% to 27% in individuals aged 80 years and older. Sociodemographic differences were found and indicated that the greatest differences in physical limitations exist between non-Hispanic whites and non-Hispanic blacks and men and women. Higher rates are also seen in adults with less than 12 years of education. Overall, these results indicate a significant increase in self-reported disability related to age, race and gender. It is also important to recognize that self-reported disability is important to individual quality of life.

The National Health and Nutrition Examination Survey (NHANES I) and the NHANES I Epidemiologic Follow-up study examined risk factors for disability in 4428 50 to 77-year-old participants.[5] This study showed that the most important baseline predictors of physical disability at 10 year follow-up were age, non-recreational activity level, history of arthritis, education, female gender and weight for height at age 40 years. Similarly, a study of 1741 University of Pennsylvania alumni between the ages of 63 and 72 years showed a postponement of disability by 7.75 years in those who exercised, had a normal body mass index and did not smoke.[9]

A chronic disease associated with multiple forms of disability in older persons is diabetes. Diabetes is a leading cause of death and by its associations with cardiovascular, neurological and ophthalmologic diseases has a significant impact on disability in the elderly. Approximately one-quarter of older men and women had diabetes in the United States in the period 2003–2006.[4] In a study of diabetic individuals aged 60 years and older from the NHANES III study, 32% of women and 15% of men reported physical limitations in walking, climbing stairs and housework compared with 14 and 8% of women and men, respectively, without diabetes.[10] As such, diabetes represents a chronic illness that makes a substantial contribution to disability in older populations.

The Lifestyle and Independence for Elders Pilot Study (LIFE-P),[11] a multicentre randomized clinical trial of individuals with functional limitations, found that adherence to a moderate-intensity physical activity intervention over 12 months showed a significant improvement in the Short Physical Performance Battery when participants performed $\geq$150 min per week of the activity. This trial indicates that physical activity interventions for previously sedentary older adults are possible and do result in measurable improvements in outcomes. This is significant because of the previously noted risks for disability with non-recreational inactivity and exercise specifically indicated in postponement of disability.

The focus of risk assessment and reduction for physical disability should occur in individuals over the age of 80 years, women, non-Caucasians, overweight/obese persons and those with less than 12 years of education. Additionally, preventive measures for disability, such as exercise, should not be limited to those without any disability. Comorbid diseases such as cardiovascular disease and diabetes should be assessed as a contributor to the disability burden in older adults. Prior disability is also significantly associated with the development of disability in activities of daily living.[12]

Mental disability often accompanies physical disability in ageing. Mental disability can be classified as major depression, dementia and vascular-related cognitive disorders. Dementia is the major contributor to mental disability because it is also associated with other mental and behavioural disturbances such as depression, anxiety and psychosis. Stroke, one of the leading causes of death and a significant contributor to the development of vascular dementia, is an important contributor to disability. Risk factors for both stroke and dementia are important targets for interventions that can decrease disability. Longitudinal studies on dementia and stroke are important stepping stones to discovering the impact and interventions. The 1987–1996 Kungsholmen Project is a longitudinal population-based study of 776 home-dwelling subjects aged 75 years and older in Stockholm, Sweden.[13] Thus far, this study has generated findings on the impact of social networks on the development of dementia. Wang *et al*.[13] suggested that frequent participation in mental, social and productive activity is associated with a lower risk of dementia in the elderly.

An unfortunate and all too common result of ageing is the loss of social ties due to death and their own or other's physical or mental disability. In addition, changing dynamics of family structure and migration contribute to this isolation. Social isolation should be recognized as a factor in an individual's overall health and quality of life. Social isolation can be considered a disability that occurs with ageing. This is an important consideration in the institutional placement of the elderly. Deciding whether placement will decrease or increase social isolation is an important consideration. Social isolation speaks of the importance of quality of life in making decisions. For example, placement of an elderly widowed male with multiple medical problems may result in loss of contact with social networks with friends and family, but may also provide a new source of social interactions.

Another type of disability is sensory disability, which includes limitations due to hearing or vision loss. These losses can often lead to deepening social isolation. The limitations can result in increased needs for an individual, medication management, special telephone service and transportation needs. These added needs represent a burden to the patient economically and psychologically. The extent of the disability can be determined by a specialist, audiologist, optometrist, or ophthalmologist. The impact that the disability has on the patient's life is what the medical professionals, for example physicians, nurses, social workers, therapists and transportation specialists, need to determine.

A specific type of sensory disability is presbycusis, sensorineural hearing loss, which can occur among older persons and may go undiagnosed and untreated. This high-frequency hearing loss with difficulty in speech discrimination often leads to further social isolation of older adults. According to the National Institutes of Deafness and Other Communication Disorders (NIDCD), 18% of American adults 45–64 years old, 30% of adults 65–74 years old and 47% of adults 75 years old or older have a hearing impairment. In addition, the NIDCD notes that 12.3% of male and nearly 14% of female adults aged 65 years and older in the United States are affected by tinnitus. Evaluations by both an otolaryngologist and audiologist are useful for determining possible causes of hearing loss and hearing aid utility.

Self-reported hearing loss and deafness have been evaluated in a number of studies. For example, the National Center for Health Statistics in the United States in 2003 found that approximately 600 000 or 0.22% of the population self-report as deaf, with more than half being over the age of 65 years. A study of the prevalence of hearing loss in a cohort of 48–92-year-olds, with an average age of 65.8 years, was 45.9%, with mild hearing loss in 58.1%, moderate loss in 30.6% and marked loss in 11.3%.[14] In addition, the percentage of people reporting a hearing handicap increased with severity of loss. The risk for hearing loss increased by 90% for every 5 years of age and men were almost four times more likely to experience a hearing loss than women. The prevalence of hearing loss among persons over the age of 85 years was 89%. These statistics indicate the vast numbers of older adults are experiencing hearing loss and associated disabilities. Health professionals must be aware of the high prevalence of hearing loss in older adults and perform hearing assessments and self-reported screenings.

Age-related vision changes include presbyopia, cataracts, diabetic retinopathy, glaucoma and macular degeneration. The loss of lens flexibility results in presbyopia. Cataracts result in clouding of the lens. Macular degeneration is the result of deposition of drusen, vascular haemorrhage and scarring. Glaucoma is the result of increased intraocular pressure. Evans and Rowlands[15] found that 20–25% of older adults in the United Kingdom have vision impairment and the majority of the impairments are correctable. This study also found that there was an association with impaired quality of life, impaired ADL performance, depression and accidents. Therefore, vision impairment represents a large

contributor to disability burden in older adults that is amenable to some correction.

Physical, mental, sensory and social disabilities culminate in increased dependence. Many of these disabilities can overlap. For example, diabetes can cause both physical and sensory disability. In addition, any sensory disability can be interpreted, without knowledge and evaluation, as confusion and lead to depression. Health care professionals bear a large responsibility in managing issues related to increased dependence, settings for optimal care and financial burden for dependent conditions. Making decisions in the elderly can be complicated due to the balance of factors that involve limiting risk and quality of life issues.

Several large-scale surveys have been used to assess disability among older adults. Friedman *et al*.[16] performed a systematic review with the aim of investigating the claims of declining disability in older Americans. The review included 16 cross-sectional and cohort survey studies published from January 1990 to May 2002. The results of this review indicated that older American adults had a significant decline in the prevalence of any disability during the 1990s and estimates of the average annual decline ranged from −1.55 to −0.92% per year. In addition, Friedman *et al*. noted that late-life disability declines were concentrated among IADL limitations and basic physical tasks. Estimates of the average annual rate of decline of the IADL limitations ranged from −2.74 to −0.40%. These changes did not include severe cognitive impairment or vision disability. No changes in hearing disability were noted.

Although it appears that increasing disability associated with ageing is being addressed on some levels, the population's continued shift will still pose many challenges. Understanding classifications, risk factors and population trends for disability are not enough. The fluid nature of disability also needs to be addressed. In a study of community-dwelling individuals aged 70 years and over, the concept of disability for ADLs was found to be of a changing and not static nature.[17] Therefore, the measurement of disability may be flawed if studies do not account for this fact. Another study, by Gill and Gahbauer,[18] examined the estimation of chronic disability using different criteria for classification that account for the malleable nature of disability. In this study, data for monthly assessments of disability in ADLs were compared with recall or anticipation of disability for ADLs over 3 months before, during or after a 54 month period. The results are consistent with the observation of a decline in disability and also an overestimation of disability in studies. As such, accounting for the changing nature of disability is important in future estimates. This is important because these estimates will be used for determining the impact of risk modification and preventative treatments on the trajectory of disability.

Interventions

Despite the deleterious effects of chronic diseases on disability and mortality, the leading cause of injury death in older persons is unintentional falls.[19] Gender differences have been found, indicating that older men are 1.5 times more likely to die from an unintentional fall than older women. The World Health Organization (WHO) identified risk factors include increasing age, decreased activity and strength, poor balance, impaired vision, osteoporosis, dementia and multiple medications/illnesses.[20] Many of these risk factors, for example, impaired vision and dementia, are also kinds of disability. In addition, some of the fall risk factors, such as level of activity, are also notable predictors of physical disability. However, many of these falls can be prevented by making changes in the physical environment, such as reducing household hazards, beginning an exercise programme to improve balance and strength and having regular health screenings to monitor medications and changes in vision. Another possibility is to wear protective hip girdles. These are interventions for disability prevention and rehabilitation.

Intervention studies for preventing physical disability are currently under way. For instance, the Lifestyle and Independence for Elders Pilot Study (LIFE-P)[11] is performing a randomized controlled trial on preserving the ability to walk in elders. This study on mobility and health-related quality of life (HRQOL) indicated the need for specific interventions for older adults at risk for disability. Community-dwelling adults with a history of falls or a risk factor for disability participated in a preventative intervention consisting of home exercise, walking exercise, group exercise and self-care exercise.[21] The intervention resulted in a significant improvement in mobility performance compared with controls. In addition, the intervention had improvement in balance performance. These results were limited by the baseline mobility and ADL performance.

Decision-making

There are several factors that are important to decision-making in geriatrics. Decision-making in geriatrics is not only important in end-of-life care but is also critical along the continuum of geriatric care. As noted already, the world population is ageing and health care is dealing with more chronic diseases and disability. The assumptions that may be made about younger patients which guide decision-making may not be applicable to older persons. Therefore, it is important to consider the various preferences that older persons may have and the challenges in providing evidence-based practices that integrate with patient preferences. Life expectancy, risk assessments and Clinical Glidepaths™[22] are useful tools in completing a full

treatment plan. Decision-making regarding risk factors for chronic disease and disability must concentrate on delaying and compressing time of disability while abiding by patient preferences. The decision-making process requires an integration of multiple factors (Figure 6.2).

Patient preferences

In a qualitative study of more than 100 practitioners, Kaufman[23] identified three problems confronted by physicians: the amount of intervention to balance risk reduction and safety and independence, advocacy for patients while demanding medication compliance and assessment of vulnerability and quality of life when making placement decisions. Developing care consistent with an individual's preferences is one facet of decision-making. Preferences may be unrealistic or possibly place an individual at increased risk for harm. How can one abide by patient preferences when these preferences are in conflict with your own or those of other family members? Can you reduce risk for disability in opposition to patient preferences? Health professionals struggle with these questions in the care of older people. Clearly, determining an individual's capacity for decision-making is critical. Do we clearly favour patient autonomy over our perceived reduction of risk? Significant time is spent reducing the perceived risks to patients, but this may not always be an efficient strategy. For example, health professionals speak to patients about decreasing tobacco and alcohol use, using assistive devices and taking medications as required contributions to risk reduction for patients. Are we really treating them or making ourselves feel better about their circumstances? Poor judgment is not the same as poor decision-making capacity. Balancing the need to treat our patients and then advocate for their wishes can be conflicting.[23]

The general definition of decision-making capacity is a patient's ability to communicate a choice and understand and appreciate the consequences of decisions, particularly decisions about medical care.[24] Ganzini *et al*.[25] noted that practitioners need further education in assessment of decision-making in different areas, mental illness and decision-making, dementia and decision-making, evaluation of cognition for determining decisional capacity, emergency treatment for patients without decision-making capacity and negative feelings towards the patient resulting in incorrect determination of decisional capacity. By determining decisional capacity, an individual's true preferences can be determined.

Shared decision-making is the ultimate goal. Unfortunately, because of clinician biases, patient disability or patient perception, older patients are less likely to participate in clinical decision-making. One study of this topic determined factors affecting goal setting, including lack of priority because of time, visits focusing on symptoms, mutual perception of disinterest in goal setting and the presumption that all patients' goals were the same.[26] Ultimately, patients needed to establish a rapport with their clinician before discussing goals. With geriatric populations, goal setting is important in the management of chronic health problems and also acute problems. Multiple studies have found that clinical goal setting is an effective method of care. As Schulman-Green *et al*. pointed out,[26] recognizing goal setting as clinically relevant makes interventions and improving knowledge of patient preferences possible.

Life expectancy and risk assessment

Screening is an important element in guiding decision-making for general medicine. However, the utility of screening among older patients yields conflicting recommendations. For many disease states, older persons have not been significantly represented or represented at all in the studies used to make guidelines. Therefore, many guidelines cannot give any recommendations for older adults, which leads to confusion in decision-making in older adults.[27] An example of this confusion is cancer screening guidelines and recommendations. Walter and Covinsky[27] offered a framework for decision-making in cancer screening that included life expectancy, risk of cancer death and screening outcomes based on published data. This framework may be applied to general risk assessment for geriatric populations. For this, one would take into account life expectancy, risk of death from the condition and outcomes data on the condition. Presumably, many of the outcomes data may not include the geriatric population, but the other elements in the framework can act as a balance in the decision-making process. Although knowing the life expectancy by the top 25th, 50th and lowest 25th percentiles gives very specific information, a general idea of life expectancy is important. For example, the Unites States vital statistics reports for 2005 note that life expectancy for men/women at 70, 75, 80, 85 and 90 years of age is 13.3/15.6, 10.2/12.1, 7.7/9.1, 5.6/6.6 and 4/4.7 years, respectively. Making some determination of a patient's general health and likelihood to live longer or shorter than expected can assist in the decision-making process. This can enhance a clinicians' ability to communicate effectively regarding relative risk assessments and determining an individual treatment plan.

Clinical practice guidelines

As just discussed, clinical practice guidelines (CPGs) or recommendations for older patients can be confusing and conflicting. What is the utility of CPGs in decision-making in the older persons? These guidelines should be based on

the latest published data about the condition. The elderly population is more likely to have multiple comorbid conditions and the practice guidelines are focused on single diseases.[28] Boyd *et al*.[29] reviewed the applicability of CPGs of the 15 most common chronic diseases to the care of the elderly with multiple comorbid diseases. The study found that most guidelines do not account for the multiple comorbidities in older patients. In addition, adherence to each guideline could result in complicated, conflicting and costly pharmaceutical and non-pharmacological treatments. This study again illustrates the complexity of decision-making in the elderly and the need for specific guidelines for the elderly. Therefore, screening recommendations and CPGs used without using specific information regarding life expectancy, patient preferences or comorbid conditions are not useful decision-making tools. CPGs are needed that include these important factors. An assessment of a clinician's quality of care of older individuals cannot be based solely on these guidelines and recommendations.

Some CPGs for non-geriatric syndrome conditions exist. For example, Brown *et al*.[30] published guidelines for older adults with diabetes and complex health status. They take a patient's financial and psychological burden, general health status and preferences into account. These guidelines included geriatric syndromes such as depression, injurious falls, incontinence, cognitive impairment and polypharmacy. Older individuals are to be screened for depression on initial diagnosis because of the increased incidence of major depression. Initial cognitive screening is also recommended because of the impact on self-care, hospitalization and association between diabetes mellitus and cognitive impairment. Screening for urinary incontinence is needed because of the increased risk factors for urinary incontinence in older individuals. A clinician then uses these guidelines in conjunction with other factors, life expectancy, overall health and preferences to reach a decision on an individualized recommendation for treatment. An algorithm[31] is shown in Figure 6.3.

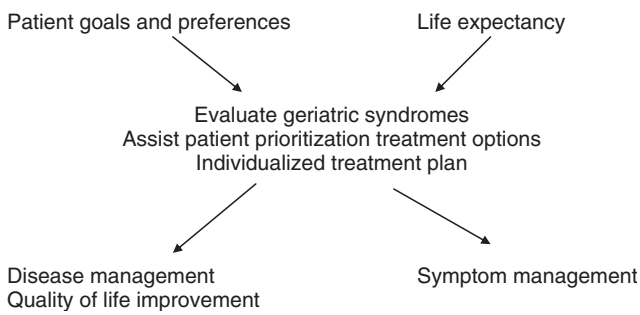

Figure 6.3 Algorithm: integrative approach to decision-making.

Quality of life measures

The WHO defines quality of life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Incorporating quality of life into clinical assessments can aid in many areas, including prioritizing problems, facilitating communication, screening for potential problems, identifying preferences and monitoring for change or response to treatment.[32] Measuring quality of life was examined in a five-article series in the *British Medical Journal* in 2001. This series examined such topics as quality of life measures, life not worth living, whether measures are patient centred and who should measure quality of life. Ideally, an individual should assess their own quality of life. According to studies, a proxy can provide a good substitute for a person who is impaired and therefore unable to complete an assessment. In general, nurses and lay caregivers can overestimate severity, whereas physicians tend to underestimate.[33] The specific measures considered should be concrete and observable to increase proxy assessments. Part of the understanding of how an individual would rate their quality of life in different situation is to understand that individuals are known to have what Sprangers and Schwartz[34] called a response shift or adaptation to their situation. This shift can result in a higher quality of life rating than would originally have been thought.

Quality of life can also be considered as the discrepancy between our expectations and experience.[35,36] Carr *et al*.[35] considered that an individual's experiences, personal characteristics such as age, social class and gender, timing of assessment and the inherent changing nature of evaluating quality of life exemplify the difficulties that arise with measurement of quality of life. Interestingly, these concepts are important not only to decision-making, but also targets for treatment. As will be discussed, this is part of the importance of the social worker and therapist in the multidisciplinary team.

Quality of life measures can be used as one of the components, representation of a patient's preferences and goals, in decision-making for an individualized disease treatment plan. As noted in Figure 6.1, this comprises part of one-third of the information needed for decision-making. The nature of these measures is flawed because of their inability to capture the full scope of individual experience.[32] Measures used should be valid, appropriate, reliable and responsive to change and interpretability. Additional properties such as simplicity, speed and ease of scoring are also important.[37] As quality of life measures are often used in research, their utility in the clinical setting can be questioned because of the different goals for their use. Existing quality of life measures available for use in clinical practice include the disease repercussion profile support team assessment schedule,

the Edmonton symptom assessment scale, the palliative outcome scale and the measure yourself medical outcome profile (MYMOP). The World Health Organization Quality of Life Instruments (WHOQOL-100 and WHOQOL-BREF) are 100- and 26-item questionnaires developed from determining important aspects of well-being from a diverse cross-section of health care professionals and patients. This measure was tested for reliability and validity in different populations.

The 'disability paradox' demonstrates that persons with significant health or functional problems do not necessarily have low quality of life scores.[35] This is probably due to adjustment of expectations and acceptance of illness. This paradox illustrates that there are individual factors that affect quality of life ratings. Therefore, it is important to decipher and prioritize what areas of life are important to one's patient. There are individualized measures such as the schedule for the evaluation of individualized quality of life (SEIQOL). The SEIQOL requires a patient to choose five areas of life that are important, choose the relative order of importance of the areas and rate their status in each area. The patient-generated index (PGI) requires a patient to identify the five areas of life affected by their current disability or health problem, rate the impact of these areas and then rate the relative importance of the five areas.

Groessl *et al*.[11] describes health-related quality of life for older adults with functional limitations. Using the Quality of Well-Being Scale – Self-Administered (QWBSA) as a measure of HRQOL, this study found that declines in mobility had a possibly greater impact on HRQOL than distinct disease states.

Outpatient Clinical Glidepaths™

The GeriMed Clinical Glidepaths are models for assisting in geriatric decision-making.[22] This concept was developed after discovering the shortfalls of evidence-based medicine clinical practice guidelines and recommendations when applied to the ageing and disabled population. Important to this concept are patient preferences and clinical experience. A dual emphasis provides guidance for providing an individualized care plan for specific disease states. Twenty-four peer-reviewed and/or evidence-based Glidepaths have been developed in the following areas: cerebrovascular accident/carotid bruit/transient ischemic attack, constipation, chronic obstructive pulmonary disease, cognitive impairment/dementia, congestive heart failure, coronary artery disease, depression, diabetes mellitus, dizziness, dyspepsia/gastroesophageal reflux disease, falls/fall prevention, focal incontinence, health maintenance, incontinence in women/men, insomnia, low back pain, osteoarthritis, osteoporosis, peripheral vascular disease, prostate cancer, syncope and weight loss. This process takes into account life expectancy by making the clinician classify the patient as robust elderly, frail, moderately demented and end of life. The robust elderly are those with a life expectancy $\geq$5 years and functionally independent. The frail have a life expectancy of <5 years or significant functional impairment. The moderately demented have a life expectancy between 2 and 10 years. End-of-life persons have a life expectancy of <2 years. In addition, patient preferences were incorporated by grading decisions as 'Do', 'Discuss', 'Consider' and 'Don't do'. These grades reflect whether the recommendation is a strong recommendation, should be discussed regarding the risk/benefit ratio, should be considered by the clinician without discussion and is not recommended, respectively.

Although the Glidepath concept incorporates many of the concepts important to medical decision-making, there are definite limitations.[22] There is no study that demonstrates improved outcomes. Many of the recommendations do not have evidence-based studies available for incorporation.

The interprofessional care team

The members of the interprofessional or multidisciplinary team are usually from diverse health backgrounds and the team composition often varies according to the clinical setting. These teams often include nurses, physicians, physical therapists, occupational therapists, speech and language therapists, recreational therapists, nutritionist/dieticians, chaplains and pharmacists. Teams exist in various permutations in primary, acute, rehabilitative and long-term care settings. These teams provide an opportunity for sharing specialized information that can aid in identifying risk factors for disability and providing input for medical decision-making. According to the framework in Figure 6.1, the team members can contribute in all three areas. The shared goal in the team should be to reach an individualized treatment plan. As such, each discipline must utilize the best available evidence, clinical judgment and patient goals/preferences to arrive at a decision. The complexity of comorbid disease conditions and disability in the ageing population is especially useful for an interprofessional team approach to decision making. In a study of the multidisciplinary needs of 1324 adult inpatients in England, the percentage of patients with multidisciplinary needs increased with age.[38] According to Hubbard *et al*.,[38] 'multidisciplinary need' was defined as needing assessment or intervention from one or more members of the multidisciplinary team on that day, other than a nurse, doctor or pharmacist. These results reflect the increase in disability with ageing and the increased need for multiple health professionals in assessing an older patient.

What is the evidence that such teams improve health outcomes, such as survival, improved function or improvement in disability or improve patient-centred decision-making? The Program of All-Inclusive Care for the Elderly

(PACE) is a model for community-based care for the frail and chronically ill elderly that utilizes the interprofessional/multidisciplinary team approach. The teams must consist of at least a primary care physician, registered nurse, social worker, physical/occupational therapist, recreational therapist, dietician, home care coordinator, personal care attendant, PACE day care centre coordinator and driver. The program assists patients eligible for nursing home placement to live independently. This program has been studied for its relative success in improving outcomes.[39] In 2009, there were 72 PACE programs in 30 states in the United States. The diversified nature of the team reflects an understanding of each team member's role in contributing to the decision-making process. The teams meet formally weekly regarding a medical crisis or health status update. The meetings are led by a team facilitator who can be from one of the disciplines and guides the thorough assessment of the patients needs. The functionality of the teams has been associated with better functional outcomes, measured by ADLs and urinary incontinence (UI), at 3 and 12 month post-enrolment intervals for patients in the PACE program. The program did not have any significant association with survival. The team functionality was determined from surveys of the team members in the 26 PACE sites included in the study. The relative agreement with seven statements in the survey was measured on a five-point scale. The statements included meeting family member needs, member contribution based on experience and expertise for quality solutions, meeting patient care needs, responding to emergencies, almost always meeting patient care needs, feeling the team's outcomes were good and the team overall functioned well together.

For a team to meet properly some of the tenets expressed in the PACE program study, the team members must possess some shared educational foundation. The Health Professionals Education Summit in 2002[40] produced five core competencies that would be essential for health professionals in meeting future health needs. Theses core competencies describe the educational needs of interprofessional team members: provide patient-centred care, employ evidence-based practice, apply quality improvement, work in interdisciplinary teams and utilize informatics. These competencies acknowledge the importance of each team member's command of their own discipline's knowledge, in addition to the ability to contribute constructively to group decision-making.

Conclusion

The ageing of the population presents unique public health and clinical challenges. However, care in preserving patient autonomy cannot be lost. The balance between our wider concerns and individual needs must be integral in the medical decision-making process. First, identifying and screening for the presence of both disability and risk factors of disability is an important task for all health care professionals. Therefore, it is important to utilize the expertise of interprofessional team members in this process. This enormous task should not be carried out by one individual. In a situation where an interprofessional team is not available, regular screening becomes more important. As noted, the fluid and changing nature of disability makes infrequent assessment inaccurate. Health professional's must be aware of this fact and encourage more frequent assessment. This will entail increased education on how to use and interpret the vast available array of assessment tools. Prevention and rehabilitation of disability should be foremost in medical decisions.

Clearly, continued population-based and basic scientific investigation is needed to elucidate further both the causes and treatment solutions for these disability states. The inclusion of older adults in longitudinal and randomized controlled trials will result in the development of more age-specific guidelines and recommendations. Irrespective of these tools, health professionals must still remember that their decisions on clinical management are for an individual and not a population. The importance of patient autonomy and preferences cannot be overstated. The team approach to decisions and solutions regarding disability can assist in this goal. Training in patient evaluation for decision-making capacity should be extended to interprofessional teams. Information that can assist a patient in participating in decision-making includes relating relevant information about your existing recommendations and guidelines, disease trajectory and life expectancy to the patient. Once a clear discussion of the relevant facts has occurred with a competent patient, decisions can be made. However, incompetent patients present obstacles to our decision-making. Health professionals should have training and comfort in utilizing a legal proxy for decision-making. Although one might look at this scenario as less than perfect, evidence indicates that proxy input is almost as good as that by the individual themselves.

Overall, the burden of disability that will come from the increased number of older adults must be addressed. A measured approach to identifying and reaching a shared decision on prevention and treatment involves the integration of multiple factors. Using the expertise and insight of multiple health professionals is likely to result in improved quality of care and outcomes.

Key points

- Disability associated with ageing.
- Prevention and treatment of disability.
- Patient preferences and goals.
- Quality of life.
- Multidisciplinary approach to decision making.

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CHAPTER 7

Social and community aspects of ageing

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Introduction

The interactions between social and community factors and access to healthcare are extraordinarily complex (Figure 7.1), especially for the older person. It is important for the healthcare professional to be aware of the impact of these factors on the health and wellbeing of the older person.

Demography of ageing

The greying of nations

The greying of nations[1] is a metaphor that describes the demographic changes that have taken place in all industrially developed countries since the beginning of the twentieth century. It describes an increase in both the numbers of older people and the proportion of the population that is older.

Absolute ageing

In both developed and developing nations, there has been a rapid growth in the numbers of older people. This has led to a need to ensure that adequate resources are available to meet the growing needs of older persons. Much effort has been placed in designing programmes that would allow older persons to remain in their own homes, 'to age in place'. These new programmes have included redesigning existing communities to deal with the problems of disability and ageing. The rate at which a nation has aged, its gross domestic product and the political will of the nation to recognize the geriatric imperative are all factors that decide the quality of life for older persons.

The causes of absolute ageing

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

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

Relative ageing

The relationship between the numbers of older and younger people in a society is important. Three factors determine the rate of relative ageing: fertility rates, mortality rates and, at a national level, patterns of migration.

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

Rising life expectancy and declining birth rate have noticeable effects on the age structure of a population. The old-age dependency ratio is the number of people aged over 65 years per 100 persons of working age (15–64 years old). Between 2005 and 2050, the old-age dependency ratio will almost double in more developed regions and almost triple in less developed regions. The socioeconomic impact resulting from this increasing old-age dependency ratio is an area of growing research and public debate. The old-age dependency ratio is most useful both for those primarily concerned with the management and planning of staff-intensive caring services and for economists and actuaries trying to forecast the financial consequences of pension policies (Figure 7.2). The demographic trend in many less developed countries has a less dramatic effect on the economic systems than in many industrial countries, primarily because less developed countries usually

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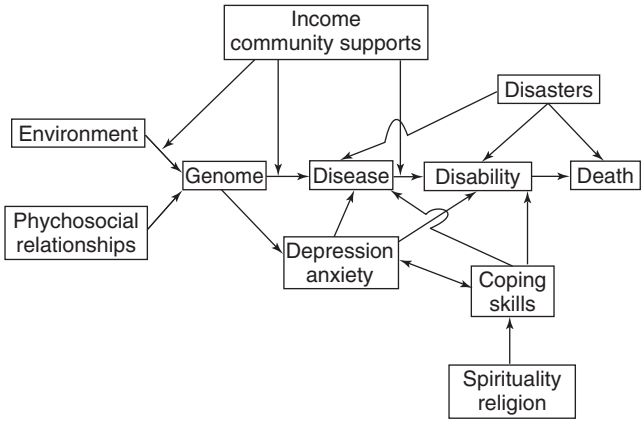

Figure 7.1 An illustration of the complex interrelationship between community/social aspects of ageing, the genome and the progression of disease and disability towards death in the older person.

have no or only rudimentary pension systems. However, the societal implication of the demographic development in these countries remains precarious, as a declining number of young people are available to take care of an increasing number of older people.[2]

Retirement migration

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

In the USA, the general trend has been a migration from colder to milder climate, especially to Florida, South Carolina, Arizona, Nevada and California. Longino[3] described migration patterns of older people in terms of three moves. The first generally occurs at retirement and involves moving for improved amenities (such as weather) and to maintain friendship contacts. The second move is precipitated by moderate functional disabilities, complicated by widowhood, and is often towards the community in which an adult child resides. The third move is due primarily to severe disabilities and is local and towards an institution such as a congregate living or custodial facility (see the section **Housing problems**).

In England, there has also been a southern migration, particularly to the southern coastal areas. People moved soon after retirement for a variety of reasons (Table 7.1). With the development of the European Union, many persons from the UK now migrate upon retirement to southern Europe.

Table 7.1 Main reasons for retirement move.

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

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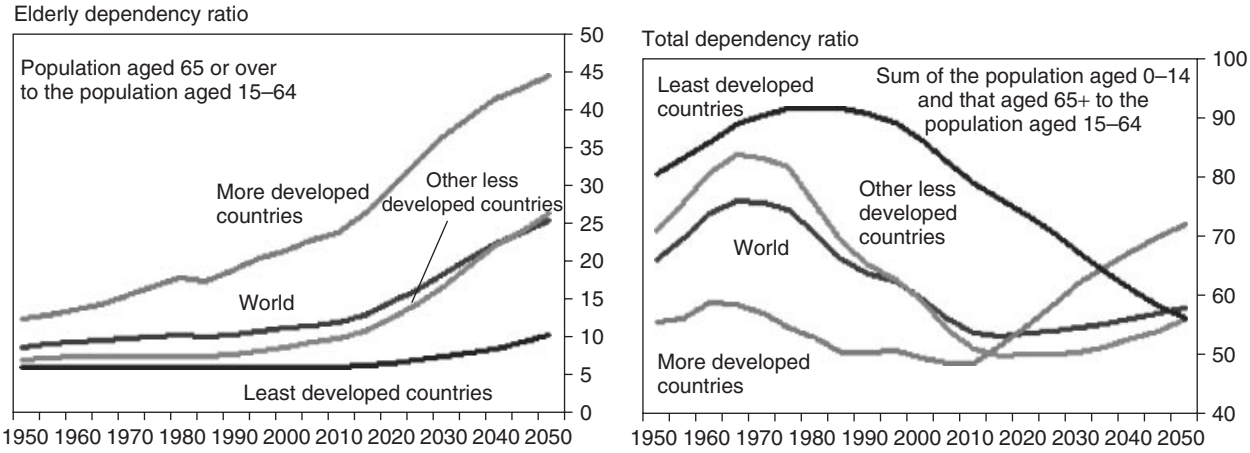

Figure 7.2 Demographic dependency ratio. Source: UN (2004 Revision).

The effect on ageing of these diverse language, cultural and healthcare systems represents a fascinating study for the future. Migration over the lifetime from a poor to a more advantaged community could improve the mortality of the migrants.

Although migration for functional elderly to better climates is on the whole positive, the development of disability often leads to frustration. With ageing and the onset of cognitive and other problems, older persons often require advocates to help them make healthcare decisions and to deal with financial problems. The loss of the ability to drive safely dictates that choosing a place to migrate to must take into account the availability of transportation and the juxtaposition of essential shopping and entertainment facilities. In the USA, case managers often assist adult children who live at a distance to provide care for their older parents who wish to remain in their homes ('to age in place'). The Community Care and Health (Scotland) Act 2002 stimulated changes in community planning for the care of older persons, including personal attendants and free nursing home care.

Effects of immigration

Two forms of immigration can affect the older person: (1) migration as an adult and (2) migration beyond pensionable age. Adult immigrants may have different rates of certain diseases in older age than the population to which they immigrated, for example, immigrants from Yugoslavia and Hungary had a higher stroke incidence than Swedes living in Malmo, Sweden.[5] Alternatively, immigration can lead to altered disease patterns. Japanese immigrants to Brazil have different cancer mortality rates than do Japanese in Japan.[6] Immigrants may or may not adapt to the diet and health practices of their host country. Older Koreans in the USA often continue to utilize traditional Korean medicine (Hanbang). Quality of life may also change. Polish-American ethnic elderly had a significantly better subjective quality of life than Polish-immigrant elderly, who in turn had a better subjective quality of life than Poles in Poland.[7] Studies of Chinese immigrants to Canada and New Zealand have suggested a high rate of depression in older Chinese immigrants compared with the general population and a similar high rate of depression is seen in Hispanic immigrants.[8]

In the USA, by 2003, 11.7% of the population consisted of immigrants. These immigrants were more likely to be poor and, as a group, earned less, had less health insurance and obtained less health promotion testing. Despite this, they live 3–4 years longer based on birth and 1.5 years longer at 65 years.[9]

Immigration has assorted effects on ageing. These may be either beneficial or deleterious. Awareness of health attitudes and health problems specific to older immigrant populations is an essential part of the therapeutic armamentarium of healthcare professionals.

Table 7.2 Expectancy of life in males and females from birth (years) (2009).

Country	Males	Females
Australia	79.2	84.1
Bangladesh	57.6	63.0
Canada	78.7	83.9
France	77.8	84.3
Germany	76.3	82.4
Israel	78.6	83.0
India	67.4	72.6
Japan	75.8	85.6
Macau	81.4	87.5
The Netherlands	76.8	82.1
Niger	57.8	56.0
Russia	59.3	73.1
Singapore	79.4	84.8
Swaziland	31.6	32.2
South Africa	49.8	48.1
UK	76.5	81.6
USA	75.6	80.0
Zimbabwe	40.1	42.6

From Wikipedia (http://en.wikipedia.org/wiki/List_of_countries_by_life_expectancy) citing CIA figures of countries by life expectancy.

The male-to-female ratio

The gender ratio of number of men to 100 women in the older age-groups is an aspect of population ageing meriting special mention. The expectation of life at birth (Table 7.2) is about 5 years greater for females in most developed countries than it is for males. In the UK, the difference between the life expectancy at the age of 60 years is about 3.5 years. In the USA, the gender ratio declines by 67% from ages 65–69 to 100+ years (Figure 7.3).

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

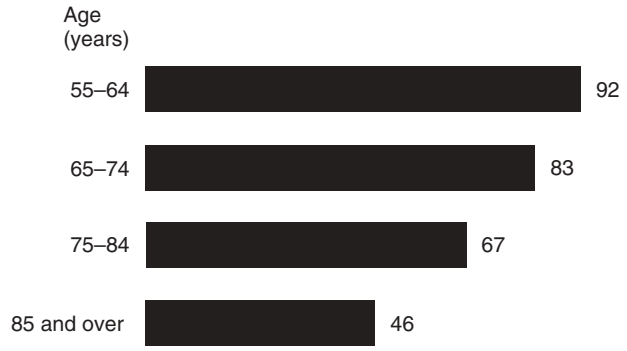

Figure 7.3 Gender ratio of people 55 years and over by age, 2002 (number of men per 100 women). Source: US Bureau of the Census, Annual Demographic Supplement to the March 2002 Current Population Surveys.

A higher death rate of men than women during Wars has also affected the ratio, while higher rates of mortality from homicide and road traffic accidents continue to have an effect during peacetime. This is particularly evident in modern Russia, where there is nearly a 12 year difference between males and females related to societal problems, following the fall of the Soviet Empire. Finally, decreased death rates during pregnancy and decreased number of pregnancies have dramatically decreased female mortality (Table 7.3).

As the lifestyles of men and women become more alike, the gap will probably narrow; changes in female morbidity and mortality associated with increased consumption of alcohol and cigarettes are trends already apparent in younger cohorts.

The changing family

The structure of the modern family in the post-industrialization period has been influenced by increased age at marriage, increased divorce rate (50% in the USA), high geographic mobility, an increasing proportion of women in the labour force and fewer children. In Europe, Asia, North America and Australia, these trends have been exacerbated in the 'baby boomer' generation (those born between 1946 and 1964).

These trends make it difficult for families to look after their elderly relatives when they become dependent. This has created the 'sandwich generation', where the middle-aged person needs to provide care for both dependent children and parents. Nevertheless, there is no evidence that the modern family in the UK or USA cares less for its elders than did the family in the past. In fact, in the USA ~80% of older persons have living children, two-thirds of whom live within 30 min of the elderly parent. Furthermore, ~75% of those over 65 years of age have some contact (personal or by telephone) each day. Support from adult children (transportation, financial and emotional) makes it possible for 95% of people aged over 65 years to live in the community.[11] Most (82%) live independently. Of those who need assistance for functional disabilities, 30% of the needs are met by family members, with the balance being met by a combination of family and formal community agency services.

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

Table 7.3 Estimated average number of children to parents born in different years.

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

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Growing older – the social process

Although the distinction is arbitrary, it is useful to try to separate the effects of physical processes affecting people as they grow older from the effects of the social consequences of attaining an advanced chronological age. There are three of these physical processes – ageing, disease and disability – and these overlap with each other and with the social process which is often called *growing old* (Figure 7.4).

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

A life course perspective on age

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

From a social psychological perspective, the transition from youth to adulthood may be seen as increasing

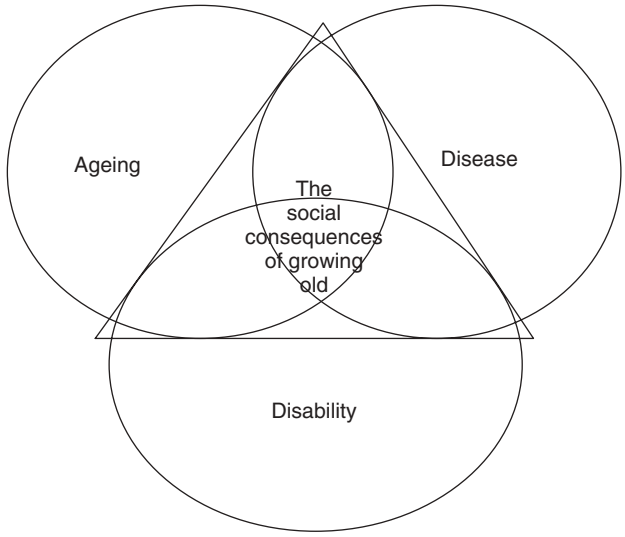

Figure 7.4 Ageing, disease, disability and the social consequences of growing old.

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

Social problems

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

The reasons why older people suffer from certain types of social problems more frequently than younger people are outlined below.

Poverty

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

Immobility

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

Attitudes of older people

Because of their upbringing, older people are, in general, less assertive than younger people. Because many were brought up in a culture in which the individual had fewer rights than they have today, many are less inclined to appeal against official decisions, to seek the help of elected representatives or to try to overcome bureaucratic inertia than younger people. In the USA, this is changing rapidly, with older persons becoming much more assertive. This began with the 'grey panther' movement and is expected to become even more prominent as the 'baby boomers' generation reaches retirement age.

Poverty

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

Poverty threshold is defined by comparing a household's income with the level of prices of the basic commodities necessary for life – the subsistence level, sometimes called the '*poverty line*' or '*bread line*'. Those whose incomes are below the minimum level necessary for subsistence are deemed to be living in poverty.

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

In the USA, the median household income in persons over age 65 years has increased from $16 882 to $23 729 (in 2006 dollars). Since the mid-1960s, poverty rates for persons aged 65 years and older have declined from nearly 30% to under 10%. Older persons now have similar poverty rates to those of working persons. Over the same period, there has been an increase in poverty rates for those under 18 years of age. Between 1984 and 2001, the median net worth of households headed by a person age 65 years or more has increased by 82%. However, older white households have nearly five times the net worth of older black households.

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

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

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

Housing problems

Environmental problems

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

There are numerous examples of major differences in lifespan in persons living in different neighbourhoods which are geographically near one another. The most marked example of this is in Scotland, where the life expectancy in Calton, a poor suburb of Glasgow, is 54 years whereas in nearby Lenzie it is 82 years. Another example is that whites living in Montgomery County, MD, have a life expectancy of 80 years compared with blacks in nearby Washington, DC, whose life expectancy is 63 years. In Canada, persons living in poor areas have more arthritis, diabetes, high blood pressure, congestive heart failure, chronic obstructive pulmonary disease and depression than those living in more affluent areas.[12] In older persons, the external appearance of the blocks they lived in and the condition of their houses were closely correlated with lower body functional limitations.[13] Perception of crime in neighbourhoods limits older persons' desire to walk outside of their houses. The problems of elderly people in city centres and areas of urban deprivation are serious and difficult to remedy because often the best remedy is a move to another area in which the person may feel equally alien, although the majority of those who move do settle well and happily.

Structural problems

Often, it is the dwelling itself that is the principal cause of the older person's concern. Common problems and their solutions are presented in Table 7.4.

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

Difficulties caused by disability

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

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

Table 7.4 Solutions to housing problems.

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

Making a move

The doctor's opinion about housing decisions is often as highly respected as his or her opinion about health decisions, particularly on that difficult decision – 'should I move?'. Although each case is unique, it is possible to list guidelines for decision-making. Tables 7.5 and 7.6 give good and bad reasons for moving. One of us (J.E.M.) uses this analogy: when living alone is no longer as safe as bungee jumping, then it is time to move to a protective environment.

In general, every attempt should be made to solve any housing problem that will remove the need for a move. The move may still happen. Children often want their parents to move before it is necessary and older adults put off the move as long as possible. The development of 'smart homes', lifeline alarms and so on are further delaying the time to when a decision has to be made to move. The decision of whether an older adult should move into a relative's home or to an institutional environment represents one of the hardest decisions associated with ageing for both the older person and the caregiver.

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

- nervous of living alone;
- anxious that they are not able to call anyone if they should fall ill;
- at risk of hypothermia or hyperthermia;
- isolated, although some people feel just as isolated in sheltered housing as in an independent dwelling.

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

Table 7.5 Bad reasons for moving.

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

Table 7.6 Good reasons for leaving.

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

Retirement

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

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

In the USA, retirement became a reality for most older persons with the introduction of Social Security. Although Social Security is the bedrock of American retirement, for many it is their pension from their employer and personal investments that have allowed earlier retirement. At

present, insecurity about the ability of the government to fund social security payments and the government health plans for the old (Medicare) and the poor (Medicaid) is creating numerous schemes on how to alter the retirement system. Some older Americans have, in retirement, been at the forefront of the modern globalization movement by retiring to Mexico or Costa Rica, where they can better leverage the buying power of the dollar.

The 'golden age' myth

Not only are modern societies those in which work is seen to be important, but they are also societies in which wealth is an important determinant of status. The low income of elderly people, therefore, not only symbolizes the low esteem in which they are held but also perpetuates it. There is a myth about old age that states that there was at one time a 'golden age' for elderly people, an age in which it was good to be old and in which elderly people were loved and respected. The myth has become elaborated with time and some people believe that the golden age was destroyed by the industrial revolution because the traditional skills of elderly men and women, which they passed on to the younger generations by the fireside and in the inglenook, were rendered redundant by the speed of change at that time.[14]

Attractive though this myth is, in fact there is no substance for it. There never was a golden age for elderly people. Rich and powerful elderly people were certainly able to hold on to their position of power and respect. Poor elderly people usually finished up in the workhouse and it is important to remember that in many societies the proportion of elderly people living in this situation was higher in times past than it is today and that the quality of care in modern institutions far surpasses that seen even a quarter of a century ago. If ever there was a 'golden age' for older persons, it is today.

Ageism

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

It is only in the last few decades that health professionals have begun to appreciate the difference between the effects of the ageing process and the effects of disease. It is extremely important to recognize that older persons, like younger persons, show large variability in most characteristics.

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

1 Failure to seek help for treatable medical problems – 'What else can you expect at my age'?

2 Failure to comply with medical advice – 'It was kind of the doctor to give me tablets but there's no point in taking them, it's just old age that's the problem'.

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

The effect of social factors on the aging process

George Valiant,[15] in his pioneering studies on ageing in Harvard graduates and inner city persons living in Boston, provided a framework for the effect of social relationships on ageing successfully (Figure 7.5). He found that not smoking, exercising, not drinking alcohol to excess, not being obese and a stable marriage were the factors that predicted successful ageing. Modern studies support the concept that social connection and perceived social support have an effect on health, but mainly in persons facing crises, stressors and/or adversity.[16] In humans, social isolation or perceived lack of social support leads to more diseases and a higher mortality rate.

Allostatic load is an index of wear and tear on the physiological systems of the body. It has been shown in a longitudinal study to be related to heart disease, physical function, cognitive function and death. The degree of allostatic load could be significantly modulated in men with strong emotional supports. This was not true in women. Other studies have demonstrated the importance of perceived control and economic variables in modulating the health effects of the social environment. This has led to the development of the concept of socioeconomic resiliency. An example of these interrelationships was shown by Suda *et al*.,[17] who found that having the person delivering meals-on-wheels sit with the older persons while they ate decreased both their nutritional risk and their dysphoria.

Figure 7.5 Effect of social relationships on ageing successfully.[15]

Thus, the effect of social relationships on an older person developing and coping with disability depends not only on the strength of the relationship but also on the ability for the person to accept the relationship (e.g. are they depressed?; or did they have a lifelong inability to bond with others?) and their innate coping skills, as well as their economic status and the inherent severity of the disease process (Figure 7.6).

Over half of men and women over 65 years of age do not engage in leisure-time physical activities. This is despite the fact that endurance and resistance exercise can modulate disease processes and slow the development of frailty, disability and death. Exercise enhances frontal lobe cognitive function and may slow the development of cerebral atrophy. Therefore, there is a need to increase the awareness of the benefits of physical activity with ageing. It is important that simple ways to improve physical fitness, for example, climbing stairs rather than taking the elevator, can be as effective as organized activities. The importance of balance exercises, such as Tai Chi, to reduce falls also needs to be stressed.

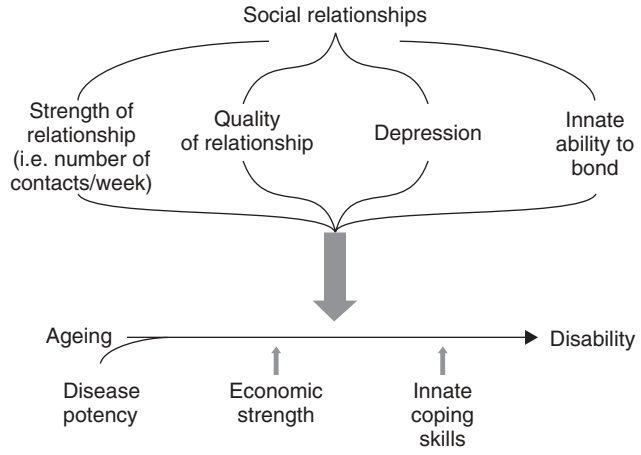

Figure 7.6 Factors modulating the ability of social relationships to modulate the ageing process.

Lifestyle, nutrition and healthy ageing: lessons from the SENECA study

The Survey in Europe on Nutrition and The Elderly: a Concerned Action (SENECA) examined lifestyle and nutrition in 19 towns throughout Europe, from Denmark to Portugal. All participants were born between 1913 and 1918. There was a large variation in lifestyle factors.[18] In Padua, Italy, 78% of older persons drank alcohol on most days compared with Culemborg in The Netherlands where less than 20% drank regularly. Smoking varied from 7% in Vila Franca de Xira in Portugal to 41% in Roskilde, Denmark. The percentage of people who still played sports varied from 4% in Portugal to 32% in Yverdon, Switzerland. Physical activity and smoking habits both predicted death and dependency. However, the relationship varied greatly from town to town, with the highest mortality rate in males being in The Netherlands, whereas the lowest death rate was in Bentanzos, Spain, a city in which the percentage playing sports was only half of that in Culemborg, but alcohol intake was nearly double. Cross-sectional studies such as SENECA represent an important tool to understand how social factors modulate disability and mortality.

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

In Hertfordshire, England, a longitudinal study found that older persons who do not smoke, have some exercise, eat five fruit and/or vegetable servings per day and drink 1–14 alcohol units per week have a 14 year physiological advantage over persons who do none of these.[19]

Religion and spirituality

Religion and spirituality play an important role in the preservation of the psychological and physical health of older persons. For example, Koenig *et al*.[20] reported that in medical inpatients religiosity correlated with a lower likelihood of feeling downhearted and blue, boredom, loss

of interest, restlessness, feeling hopeless or feeling as if other people were better off. Brown and Gary[21] found that fewer depressive symptoms were associated with religious involvement in a group of urban African-American males. In Israel, religious orthodoxy was found to be protective against death from coronary heart disease, independent of lifestyle correlates. Lack of comfort from religion and failure to participate in church events was associated with an increase in death following heart surgery. In patients with lung cancer, prayer was, in part, responsible for psychological wellbeing.[22] Positive religious coping methods were found to be associated with health improvements. On the other hand, persons who were not at peace with religious issues, or saw God as punishing, had worse outcomes. Spirituality in the UK was shown to be a significant predictor of psychological wellbeing in frail older persons. Spirituality, but not religiosity, was associated with self-appraised good health. Spirituality is associated with a greater ability to deal with grief. In non-Judeo-Christian cultures, the role of spirituality is less clear; a study in Japan showed mixed effects; spirituality was positive in Thais. Religious television or radio was associated with worse physical functioning and greater medical comorbidity.[23] In a meta-analysis, weekly attendance at religious services was slightly more cost-effective than statin use.[24]

Overall, the role of religion and spirituality can be summarized as predominantly improving psychological health with a lesser effect on physical health. There is a small literature suggesting that not all forms of religion are positive. The most parsimonious model for describing the role of religion and spirituality on health is to assume that it increases coping skills and enhances access to support groups.

Healthcare professionals need to be aware of the religious and spiritual affiliations of their patients and, in appropriate cases, be prepared to incorporate them into a holistic model of healthcare. Prayer is a commonly used coping strategy for many older persons dealing with disability or life-threatening illnesses. Involvement of a person's religious leader as part of the team approach to healthcare is important. In some countries, this may stretch to the need to involve the local shaman in the healthcare team.

Anti-ageing medicine

Since the beginning of time, persons have sought the mythical fountain of youth.[25] This has led over the centuries to numerous unscrupulous people selling their version of 'snake oil' to vulnerable older persons. Within recent times, pseudoscientific claims associated with the growth hormone and dehydroepiandrosterone as agents that will 'reverse the ageing process' regularly appear in newspapers, magazines and books. Many of these claims are based on flawed studies originally published in mainstream medical journals. Others are based on hypotheses developed by scientists and published in mainstream literature and then translated as fact by the lay press. A example is the theories of Aubrey de Grey, which are futuristic and not yet ready for 'prime time'.[26] In a 2003 book, Ronald Klatz and Robert Goldman claimed that 'the future of anti-aging medicine promises the elimination of the disability, deformity, pain, disease, suffering and sorrow of old age. In a few decades, the traditional enfeebled, ailing elderly person will be but a grotesque memory of a barbaric past'.[27] Hyperbole such as this is reminiscent of the popular book *The Art of Living Long*, written by the Italian Luigi Comaro in 1550.

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

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

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

The environment and the genome

There is an increasing literature demonstrating that the environment can modulate gene expression. Two examples of the environment interaction have been found with the APOE4 gene: (1) head injury accelerates Alzheimer's disease in persons who have the APOE4 allele;[28] (2) APOE4 is a risk factor for ischaemic heart disease predominantly in smokers.[29] The interaction of a major life event with a genetic predisposition increases the likelihood of major depression. Physical exercise produces different responses depending on the person's angiotensin-converting enzyme insertion deletion genotype.

Epigenetics represents an emerging area where the environment can alter the genome. Genes can be modulated in response to diet and environmental stressors through DNA methylation, chromatin remodelling, production of double-stranded RNA and prions. These changes continue into old age. There is emerging evidence suggesting that epigenetic changes may be responsible for some forms of mild cognitive impairment.

Similarly, the development of pharmacogenomics has shown that the efficacy and side effects of drugs are associated with specific alleles. For example, persons with the

apolipoprotein E allele have different responses to the antidepressant paroxetine, dependent on the allele.[30] Side effects from paroxetine are related to the number of C alleles of HTR2α.

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

Elder abuse

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

The Internet

Although older persons have traditionally been much less likely to use the Internet than are middle-aged adults or children, this is changing rapidly. Many nursing homes offer Internet facilities for older persons to communicate with family and also to access the news. Older persons are also using the Internet to obtain healthcare information.

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

Cultural competency

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

Disasters

The recent spate of earthquakes worldwide in early 2010 served as a reminder of the devastating effects of disasters. In all disasters, older persons are disproportionately affected. Studies in North Africa have shown that older persons are more likely to be left behind when genocide occurs and younger persons flee, creating separation between the generations. Older persons are also more likely to die during migrations from enemy troop areas and during periods of famine. In developed countries, heat waves are the most common disaster causing death. Over 400 older persons per year die from heat-associated death in the USA. Heat waves are often associated with power outages, which lead to air conditioning being unavailable. This has been characterized as a 'disaster within a disaster'. The appropriate measures for preventing heat-related deaths are outlined in Table 7.7.

During disasters, such as hurricanes and earthquakes, one-third of older persons have a worsening of their medical conditions. The disruption of services following these disasters can lead to isolation of the older person, loss of home services and loss of access to prescription medicines. The appropriate contents of a disaster kit for older persons are listed in Table 7.8. Following disasters, there is an increase in myocardial infarctions. For example, the Hanshin–Awaji earthquake in Japan was associated

Table 7.7 Preventing heat-related deaths.

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

Table 7.8 Items to be included in a senior disaster preparedness kit.

- Identification bracelet
- Extra pair of glasses/hearing aids
- List of medications
- List of diseases
- Set of emergency prescriptions
- 3 days to 1 week medication supply
- Flashlight
- Extra batteries
- Pet evacuation plan
- Family pictures
- Emergency numbers (including a contact for at least one family member who lives in another geographical area)
- A copy of FEMA's *Are You Ready?* emergency preparedness handbook
- A copy of the Hartford Foundation's *The Calm Before the Storm* for family members of patients with dementia

with a threefold increase in myocardial infarctions. The earthquake in Chengdu, China, was associated with a doubling of the death rate in persons over 90 years of age. Even psychological stressors such as the return of Hong Kong by the British to China increased mortality rates in old men. The reverse is also true, in that, when there is a reduction in environmental stressors such as when East Germany reunited with West Germany there was a marked improvement in longevity in East Germans.

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

Terrorism affects many countries. While a bombing incident is easily recognized, there is a need for surveillance techniques to detect outbreaks of disease, as was shown in the slow recognition of the *Salmonella* outbreak by the terrorist cult in Oregon in 1980 and the anthrax outbreak in the USA in 2001. The anthrax outbreak demonstrated that older persons had a greater susceptibility to biological agents and a poorer outcome than young persons. Terrorist attacks may include (1) biological agents, for example, smallpox, ricin, anthrax, plague, *Salmonella*, ebola; (2) chemical agents, for example, vesicants (blistering agents) such as lewisite or mustard gas or cholinesterase inhibitors from the G group (GB-Sarin, GD-Soman) or the V-group (VX); (3) nuclear weapons or attacks on nuclear power plants or nuclear waste transport systems. The symptoms produced by cholinesterase inhibitors are listed in Table 7.9.

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

Table 7.9 Symptoms produced by cholinesterase inhibitors.

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

Key points

- Genome–environmental interactions play an important role in the development of disease and disability with ageing.
- Disasters have a disproportionate effect on older persons.
- Religion and spirituality have positive effects on ageing.
- Immigrants live longer than non-immigrants, despite multiple stressors including a higher level of poverty.

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CHAPTER 8

The developmental origins of ageing

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Introduction

> As soon as we are born we begin to die and the end depends on the beginning.
>
> *Manilius Astronomica*, IV 16

Interest in the connection between development, growth and ageing is not new. Animal studies linking rate of growth and length of life date back to the 1930s. Early findings, however, were conflicting and demonstrated both beneficial and detrimental effects of growth restriction on lifespan. Only later was it understood that timing of the dietary intervention to reduce growth was critical; dietary restriction in later life could slow ageing processes and extend lifespan, whereas a similar intervention instituted in prenatal life was associated with adverse effects.[1]

Human ageing can be studied at a number of levels, from a population approach down to investigation of individuals at a system or cellular and molecular level. The ageing of a population is defined in terms of mortality statistics, but individual ageing may be defined more broadly as the deteriorative changes with time during post-maturational life that underlie an increasing vulnerability to challenges, thereby decreasing the ability to survive. Progress in understanding why ageing occurs has come from the field of evolutionary biology and there is growing support for the concept that failure of repair is central to ageing. Aetiological studies of ageing have traditionally focused on influences operating in later life, but this has been extended to consideration of the role of early environmental factors, particularly on age-related disease and mortality. More recently, there has been research investigating the developmental origins of system ageing and preliminary studies identifying underlying cellular and molecular changes.

The influence of early nutrition on subsequent health and disease has been a focus of dietary manipulation studies in a range of animal models, but human studies have generally utilized birth characteristics such as size at birth or in infancy as markers of early nutrition and related these to subsequent health outcomes. However, there is also some evidence for the direct effects of early nutrition on long-term human health from natural experiments such as the Dutch Famine Study. This chapter introduces the underlying concept of developmental plasticity and presents evidence for links between birth characteristics and mortality, age-related disease, ageing at a system level (illustrated by the musculoskeletal system) and ageing at a cellular and molecular level. The final section proposes a life course approach to ageing and the relevance of this to clinical practice.

Developmental plasticity

A series of epidemiological studies demonstrating the relationship between small size at birth and an increased risk of age-related disease in later life led to the developmental origins of health and disease hypothesis.[2] Initial observations came from geographical studies. For example, Forsdahl reported that the prevalence of arteriosclerotic heart disease correlated with past infant mortality in the 20 counties of Norway and was the first to suggest that a poor standard of living in childhood and adolescence was a risk factor in heart disease.[3] A subsequent study showed that differences in rates of death from coronary heart disease in different parts of England and Wales paralleled previous differences in death rates among newborn babies.[4] This led to the Barker hypothesis that adverse environmental influences *in utero* and during infancy permanently change the body's structure, physiology and metabolism, increasing susceptibility to disease in later life.

The developmental origins of health and disease are thought to be a subset of the broader biological process of developmental plasticity by which organisms adapt to the environment experienced across the life course. Developmental plasticity involves a single genotype producing alternative forms of structure or function in response to environmental conditions, and it appears to have evolved

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because it is adaptive. It promotes Darwinian fitness by enhancement of survival and reproductive success through enabling a range of phenotypes better suited to both the prevailing environmental conditions and the anticipated future conditions.[5] The biological basis for invoking developmental plasticity as an influence on the risk of disease derives from animal studies in which dietary, endocrine or physical challenges at various times from conception until weaning induce persistent changes in cardiovascular and metabolic function of the offspring. The most commonly used animal models involve a prenatal nutrient imbalance which can be induced by a reduction in overall maternal food intake or by protein restriction in an isocaloric diet. Other models include non-nutritional interventions such as glucocorticoid exposure or placental restriction to impact on early growth and development.

There is growing evidence that epigenetic mechanisms are responsible for tissue-specific gene expression during differentiation and that these mechanisms underlie the processes of developmental plasticity. Examples of epigenetic mechanisms include coordinated changes in the methylation of cytidine–guanosine (CpG) nucleotides in the promoter regions of specific genes, changes in chromatin structure through histone acetylation and methylation and post-transcriptional control by microRNA. Cues for plasticity operate particularly during early development and they may affect a single organ or system, but generally they induce integrated changes in the mature phenotype. In mammals, an adverse intrauterine environment, including suboptimal nutrition, results in an integrated range of responses, suggesting the involvement of a few key regulatory genes that reset the developmental trajectory in expectation of poor postnatal conditions. Mismatch between the anticipated and the actual mature environment exposes the organism to risks of adverse consequences. For humans, it is suggested that prediction is inaccurate for many individuals because of changes in the postnatal environment towards energy-dense nutrition and low energy expenditure, contributing to the epidemic of age-related disease.

Developmental influences and mortality

Geographical studies demonstrated that areas with high infant mortality were also the areas with high mortality from coronary heart disease 70 or more years later. However, it took retrospective cohort studies to demonstrate the link between birth characteristics and adult mortality in individuals. This required identification of men and women with historical records of early size. This could then be related to the later occurrence of age-related disease. The first study of this kind was carried out in the county of Hertfordshire, UK. From 1911 onwards, all births were attended by a midwife who measured birth weight. Subsequently, a health visitor went to the baby's home at intervals throughout infancy and the weight at 1 year was also determined. This information was meticulously recorded in ledgers (Figure 8.1). Many years later, the individuals in these records were traced, enabling the relationship between size at birth or infancy and subsequent health to be investigated.

The associations between birth weight and a range of mortality outcomes have been considered in the Hertfordshire Cohort Study.[6] This included 37 615 men and women born in Hertfordshire, UK, between 1911 and 1939, of whom 7916 had died by the end of 1999. For men, lower birth weight was associated with increased risk of mortality from circulatory disease [hazard ratio per standard deviation decrease in birth weight 1.08, 95% confidence interval (CI), 1.04–1.11] and from accidental falls, but with decreased risk of mortality from cancer (hazard ratio per standard deviation decrease in birth weight 0.94, 95% CI, 0.90–0.98). For women, lower birth weight was associated with a significantly ($p < 0.05$) increased risk of mortality from circulatory disease, injury, musculoskeletal disease, pneumonia and diabetes. Overall, the beneficial effects of an increase in birth weight outweighed the detrimental effects, such that a one standard deviation increase in birth weight reduced all-cause mortality risk by age 75 years by 0.86% for both men and women.

It has been postulated that suboptimal early nutrition underlies the association between low birth weight and increased mortality in adult life. Evidence from the few animal studies that have investigated the effect of dietary restriction during prenatal or early postnatal life, as opposed to post-maturational life, supports this. For example one study of mice dating back to 1920 showed that alteration of diet shortly after birth, sufficient to slow growth, resulted in a shorter lifespan. More recent work using a rat model investigated the effect of a maternal low protein diet on mortality of the offspring. Rat dams were fed either a control diet or a low protein diet from conception until the end of pregnancy. The average lifespan of the female rats exposed to a low protein diet in utero was reduced by 11%[7]. There was a similar but non-significant trend in the males. Two subsequent studies using rat models also found that that prenatal dietary restriction was associated with a shorter lifespan.

Developmental influences and age-related disease

The epidemiological studies demonstrating links between weight at birth and adult coronary heart disease mortality have been followed up by cohort studies of survivors where

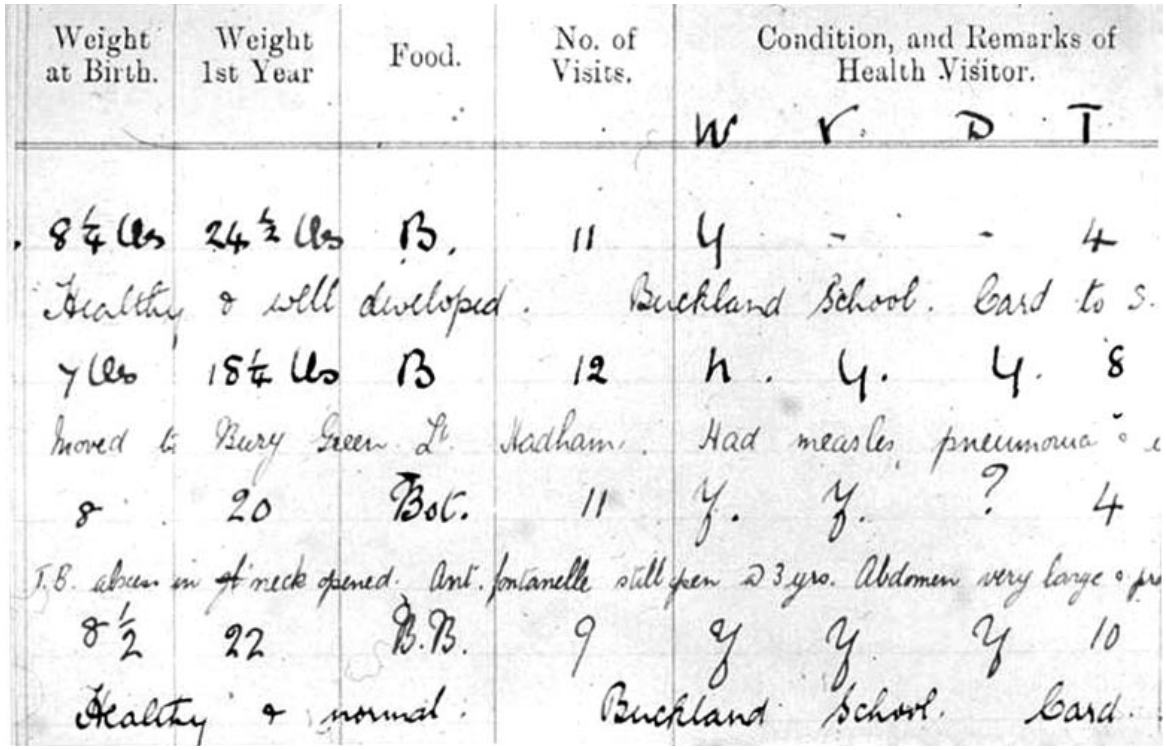

Figure 8.1 Historical ledger from Hertfordshire, UK.

the prevalence of heart disease as well as its risk factors could be identified. Low birth weight has consistently been shown as a risk factor for coronary heart disease and stroke in studies from different populations in Europe, North America and India. The relationship is not limited to the extremes but is graded and linear, operating across the range of normal birth weights. There is some evidence that prematurity is associated with at least some of the risk factors for heart disease but most of the population-attributable risk is thought to be due to reduced fetal growth independent of gestation. Furthermore it appears that the important developmental phases affecting long-term cardiovascular health extend into infancy and childhood.

The association of low birth weight and higher blood pressure is modest, approximately 2 mmHg per kilogram birth weight, whereas the association with frank hypertension is stronger and has been attributed in part to the number of nephrons or the amount of elastin in blood vessel walls, which are lower in individuals born small. There is also evidence that the shape and size of the placenta are important for the subsequent development of hypertension and cardiovascular disease. For example, in the Helsinki Birth Cohort, a small placental surface area was associated with the later development of hypertension in shorter mothers.[8] It has been suggested that the effects of placental area on hypertension depend on the mother's nutritional state. Poor maternal nutrition may compound the adverse effects of small placental size. In better nourished mothers, the placental surface may expand to compensate for fetal undernutrition. They may also reflect effects of the mother's body size on the transport of nutrients across the placenta.

Small size at birth, in terms of both thinness and low birth weight, has been consistently associated with type 2 diabetes and impaired glucose tolerance. However, in some studies, an inverse J-shaped association has been shown with rates again increasing at the highest birth weights. It has been suggested that gestational diabetes, which is associated with high birth weight, may itself programme long-term adverse health outcomes. Insulin resistance is thought to be a consequence of the term changes in body composition associated with low birth weight, in particular the combination of low lean mass with high fat mass. The relationship between low birth weight and plasma lipids is relatively small: two recent meta-analyses have reported an overall association of approximately $0.04\,\text{mmol}\,\text{l}^{-1}$ higher total cholesterol per kilogram lower birth weight. However, birth weight is only a crude indicator of adverse environmental conditions such as suboptimal nutrition. For example, the Dutch Famine Study showed that famine during early gestation was associated with an atherogenic lipid profile despite being unrelated to birth weight.

Developmental influences and ageing of the musculoskeletal system

Musculoskeletal ageing is a key contributor to the development of physical frailty, disability and dependency in later life. Most aetiological research has focused on identifying adult influences on ageing in the different components of the musculoskeletal system, but recent attention has focused on the contribution of developmental plasticity to ageing in skeletal muscle and bone.

Skeletal muscle ageing

Skeletal muscle makes up 40–50% of the human body. It consists of longitudinally arranged muscle fibres broadly classified into two main groups illustrated in Figure 8.2. Type I myofibres have a high capacity for oxidative phosphorylation with high myoglobin levels and mitochondrial density. They are used for endurance activities and are characterized by a slow contraction time and relative resistance to fatigue. Type II myofibres have a greater reliance on glycolytic enzymes. They are used for short, powerful bursts of movement and typically have a fast contraction time but tend to fatigue rapidly. There are multiple changes in muscle with age. Macroscopically there is a reduction in muscle mass with infiltration of adipose and connective tissue. Microscopically there is a reduction in the myofibre number and cross-sectional area, particularly affecting the type II fibres. At the molecular and cellular level, there is decreased muscle protein synthesis with evidence of reduced mitochondrial activity and increased oxidative stress.

The loss of muscle mass and function with age is called sarcopenia and there is increasing recognition of its adverse consequences in terms of increased disability, morbidity, mortality and health care costs. Adult determinants of sarcopenia, including age, gender, size and level of physical activity, have been well described and the beneficial effect of resistance exercise to slow the age-related loss of muscle has been well documented. Twin studies suggest a heritable component and a recent genome-wide association study identified *TRHR* as an important gene for lean body mass. Nevertheless, there remains considerable unexplained variation in muscle mass and strength between older people which may reflect not only the current rate of loss but also the peak attained earlier in life. Early growth and development of muscle are important determinants of peak muscle mass and strength which are achieved in early adulthood and generally remain stable until the fifth decade. Over the age of 50 years, muscle mass is lost at a rate of 1–2% per year and strength at 1.5–3.0% per year.

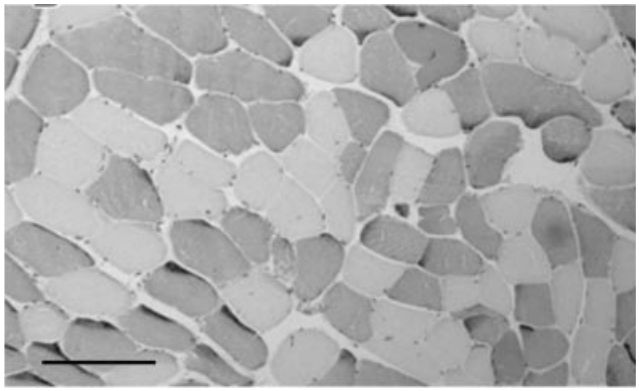

Figure 8.2 Cross-section through muscle fibres.

Evidence for developmental influences on ageing muscle has come from a series of observational epidemiological studies linking low birth weight with reduced muscle strength, mass and size in later life. The association between low birth weight and reduced muscle strength was first reported in the Hertfordshire Ageing Study, a retrospective birth cohort study of men and women born in Hertfordshire, UK, between 1920 and 1930 and still living there 60–70 years later.[9] They had historical health visitor records of weight at birth and age 1 year and were traced through the National Health Service Central Registry in Southport, UK. Following a home interview, 717 men and women attended a local clinic for measurement of current size and markers of ageing in different body systems, including grip strength measured using hand-held dynamometry (Figure 8.3). Lower birth weight and weight at 1 year were significantly associated with lower grip strength in later life. These relationships remained significant although attenuated after allowing for adult height, suggesting that an adverse early environment may have an effect on both muscle quality and quantity.

The association between birth weight and adult grip strength has been replicated in a younger group of Hertfordshire men and women born in 1931–1939 and participating in the Hertfordshire Cohort Study and in a British birth cohort of middle-aged men and women born in 1946 and taking part in the National Survey of Health and Development. More recent work has demonstrated a similar effect of size of birth weight on adult muscle strength in young women aged 20–34 years taking part in the prospective Southampton Women's Survey, suggesting that the association may be between birth weight and peak muscle strength rather than decline. Using a meta-analysis approach, it has been possible to compare the findings from published epidemiological studies investigating the relationship between lower birth weight and reduced grip strength in later life. These show remarkable homogeneity of association with a pooled effect size estimate of a 2.06 kg increase in grip strength per kilogram increase in birth weight. Adult height typically attenuated, but did not

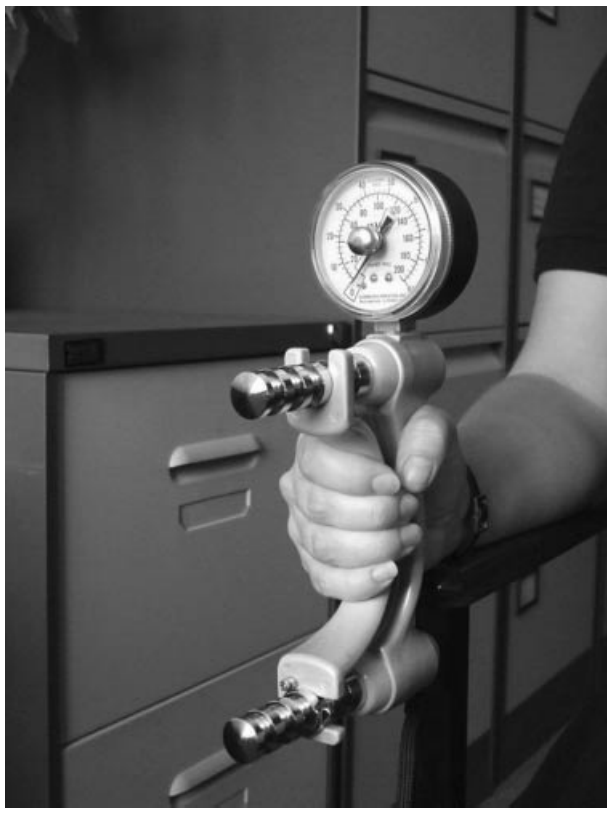

Figure 8.3 Grip strength measured using hand-held dynamometry.

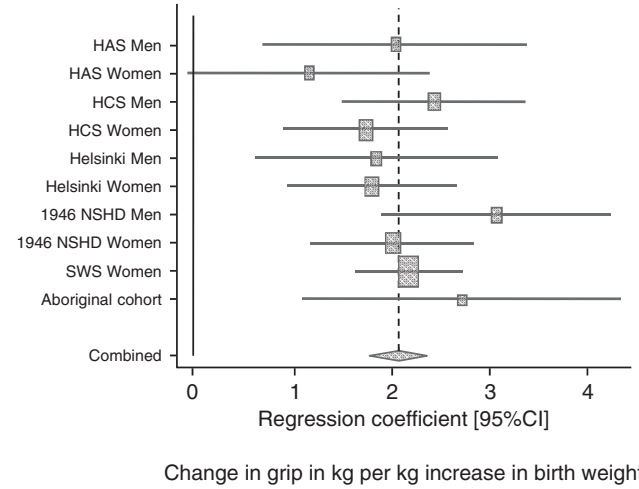

Figure 8.4 Meta-analysis of the association between birth weight and grip strength. Reproduced from Sayer *et al.*,[10] with permission from Springer Science + Business Media.

remove, the birth weight versus grip strength relationship (Figure 8.4).[10]

Studies investigating the relationship between growth in early life and muscle mass have demonstrated consistent findings linking low birth weight with reduced muscle mass. A study of older men participating in the Hertfordshire Cohort Study showed that birth weight was strongly positively associated with fat-free mass but showed only weak positive associations with measures of adult total fat mass. In contrast, weight at the age of 1 year was strongly associated with fat-free mass and adult fat mass estimated using anthropometry. Similar findings were observed in studies of men and women using urinary creatinine excretion and dual X-ray absorptiometry to estimate muscle mass. A study in the Helsinki Birth Cohort has replicated the relationships between small size at birth, lower muscle mass and reduced grip strength in adults. More recent work using peripheral quantitative computed tomography to measure muscle size directly has shown that birth weight is positively associated with forearm and calf muscle area in older men and women, suggesting tracking of relative muscle size throughout life.

There is considerable interest in which early environmental influences are important in these epidemiological associations. Few retrospective cohort studies have sufficiently detailed data on pre- and postnatal environmental influences to assess specific effects on long-term muscle mass and strength. However, the prospective cohort design of the Southampton Women's Survey will allow these questions to be addressed.[11] This study has recruited over 12 500 women living in the city of Southampton, UK, and interviewed them to assess general health, body composition, lifestyle and diet. The women have been followed up during pregnancy and their offspring studied through childhood, with the aim of identifying prospectively the influence of the preconceptional and antenatal environment on the growth and development of the fetus and child. Using data from 448 mother–offspring pairs in this cohort, it was possible to examine maternal influences on neonatal body composition ascertained by dual X-ray absorptiometry.[12] Taller women and those with higher parity had offspring with increased birth weight, fat and lean mass, whereas women who smoked during pregnancy had lower birth weight babies, with reduced fat and lean mass. Maternal walking speed as a marker of maternal physical activity was negatively associated with birth weight and maternal fat mass positively predicted neonatal relative fat but was negatively correlated with proportionate lean mass.

Bone ageing

Close relationships between muscle and bone mass have been documented at different stages of life and a number of studies have considered this association during musculoskeletal ageing. A Finnish study of peri- and post-menopausal women demonstrated that women who experienced an improvement in grip strength over a 5 year

period had significantly lower rates of bone loss at the femoral neck and lumbar spine compared with those whose grip strength remained unchanged or decreased.[13] A study utilizing the Framingham Heart Study Cohort of 504 women and 285 men aged 72–93 years reported that among men, muscle mass and not percentage fat was positively associated with bone mineral density; among women, bone mineral density increased with both increasing muscle and fat mass.[14] There is considerable interest in what might underlie the relationship between ageing bone and skeletal muscle. There is some evidence for muscle contraction as an important mechanical stress for increasing bone density, but the role of shared developmental influences remains to be explored.

Ageing is associated with bone loss and osteoporosis, which is a skeletal disorder characterized by low bone mass and microarchitectural deterioration. Osteoporosis is a major cause of morbidity and mortality through its association with age-related fracture. The worldwide direct and indirect annual costs of hip fracture in 1990 were estimated at US$34.8 million and are expected to rise substantially over the next 50 years. These fractures typically occur at the hip, spine and distal forearm. The frequency of fracture at all three sites increases with age and fracture pathogenesis depends upon both bone strength and propensity to trauma. Bone strength is directly related to bone mass; the bone mass of an individual in later life depends upon the peak attained during skeletal growth and the subsequent rate of bone loss. Although there is evidence to suggest that peak bone mass is inherited, current genetic markers are unable to explain more than a small proportion of the variance in individual bone mass and determinants of bone loss are incompletely understood. However, evidence is accumulating that early environmental influences also modulate peak bone mass and fracture risk.[15]

Several epidemiological studies have addressed the relationship between birth weight, weight in infancy and bone mass in adulthood. In the first of these, 153 women born in Bath, UK during 1968–1969 were followed up at age 21 years; data on childhood growth were obtained from linked birth and school records. Statistically significant associations were documented between weight at 1 year and bone mineral content, but not density, at the lumbar spine and femoral neck. These relationships were independent of adult body mass index. The findings were replicated in an older cohort of 238 men and 201 women aged 60–75 years in Hertfordshire, UK. Again, the relationship remained after adjustment for later environmental determinants of bone loss such as physical activity, dietary calcium intake, cigarette smoking, alcohol consumption and age at menopause among women. These studies have also provided evidence that the early environment might interact with the genome in influencing bone mass. Thus, polymorphism in the gene for the vitamin D receptor was shown to relate to bone mineral density in opposite directions among individuals of varying birth weight. Among individuals with the 'BB' genotype, lumbar spine bone mineral density was increased in those of lower birth weight but reduced in those of higher birth weight. Such findings suggest that genetic influences on adult bone size and mineral density may be modified by understanding early growth and development.

Confirmation of these observations in the United States, Scandinavia and Australia allowed the data relating growth in infancy with adult bone mass to be brought together.[16] This demonstrated that the strongest association was between weight in infancy and adult bone mass, with around 50% of this relationship observable by birth. However, the clinically important consequence of reduced bone mass is fracture and there are also data directly linking growth rates in childhood and adolescence with the risk of later hip fracture.[17] A study in the Helsinki Birth Cohort allowed linkage of birth and growth data to later hospital discharge records for hip fracture in 7000 men and women born in 1924–1933. The two main determinants of hip fracture risk were tall maternal stature and low rate of weight gain between age 7 and 15 years. In addition, those with fracture were found to be shorter at birth but of average height by age 7 years, suggesting that hip fracture risk might be particularly elevated among children in whom growth of the skeletal envelope was forced ahead of the capacity to mineralize. Extrapolation from the epidemiological studies of bone mass to those of hip fracture suggest that developmental plasticity of bone mass alone would be insufficient to explain the hip fracture risk. It is likely that developmental influences on muscle mass and strength are also involved and that ageing of the musculoskeletal system as a whole needs to be considered in the aetiology of fracture in older people.

The associations between birth characteristics and musculoskeletal ageing have been clearly demonstrated. However, the causal pathways are only just starting to be investigated. Detailed physiological studies have been used to investigate hormonal influences and the role of the hypothalamic–pituitary–adrenal axis. Profiles of circulating cortisol and growth hormone were obtained in groups of men and women and related to both size in early life and adult bone density. These studies showed that low birth weight predicted increased adult cortisol levels and low weight in infancy was associated with decreased growth hormone levels in later life. The levels of these two skeletally active hormones were also found to be determinants of prospective bone loss. The data are compatible with the hypothesis that environmental stressors, such as undernutrition, occurring during intrauterine or early postnatal life, may alter the sensitivity of the growth plate to cortisol and growth hormone. The consequence of this endocrine programming would be to reduce peak

skeletal size and perhaps also mineral density, and also to predispose individuals to accelerated rates of bone loss during later life. The role of the resetting of endocrine axes in linking birth characteristics with muscle ageing remains to be established.

Developmental influences and ageing at the cellular and molecular level

Cellular and molecular ageing mechanisms

There is growing acceptance for the disposable soma theory of ageing,[18] which comes from the field of evolutionary biology. This proposes that our survival mechanisms, which evolved to cater for the shorter lifespans of our evolutionary ancestors, are insufficient to prevent damage from accumulating over the longer term. Ageing is therefore caused by the lifelong accumulation of subtle cellular and molecular faults – a process that might begin *in utero*. Multiple mechanisms are likely to contribute to the accumulation of damage that causes ageing and conversely there are multiple maintenance and repair systems in place to counteract them. It has been proposed that the genetic setting of the maintenance and repair systems explains the genetic contribution to human ageing.

There is considerable interest in understanding the specific cellular and molecular mechanisms underlying the process of ageing in both stem and non-stem cells and much of the focus of current research is on the role of nutrient sensing pathways,[19] reactive oxygen species (ROS) production[20] and DNA damage and repair.[21] ROS are byproducts of energy-generating mitochondria and cause damage to both mitochondrial and nuclear DNA, including telomeres. Telomeres are non-coding DNA repeat sequences at the ends of chromosomes that decrease in length during each cell division. When they become critically short, the cell is no longer able to replicate and enters cellular senescence. Telomere shortening is accelerated by oxidative damage and has been proposed as a biomarker of human ageing. Sirtuins may link nutrient sensing, ROS production and DNA damage/repair. They are intracellular proteins that have an important role in nutrient sensing pathways and may also be involved in DNA repair. Caloric restriction, the only intervention to prolong lifespan consistently across species, is associated with increased levels of sirtuins and a number of studies have investigated the effects of giving resveratrol, found in red grapes, as it mimics sirtuin activity.

Increasingly studies of ageing at the molecular and cellular level are being linked to ageing at the system level. In ageing muscle there has been considerable investigation of the role of nutrient sensing, ROS production and DNA damage/repair at the molecular level and also study of the loss of muscle fibres and stem cells at the cellular level.[22] It has been proposed that the decline in muscle mass and strength with age is associated with impaired insulin signalling, decreased protein synthesis and aberrant ROS generation. In bone, there have been several studies investigating the relationship between telomere length and bone ageing. One recent study found a significant association between telomere shortening and reduced bone density in female twins. However two subsequent studies failed to replicate these findings. A study of organ-specific telomere shortening in a rat model demonstrated age-dependent shortening in the kidney, liver, pancreas and lung but not the brain; muscle and bone were not studied. A study using a mouse mesenchymal cell line considered the role of sirtuins and demonstrated that a sirtuin was expressed in stem cells and furthermore that resveratrol, which activates Sirt1, led to increased expression of osteoblast markers and increased mineralization.

Developmental influences on general mechanisms of ageing

Understanding of developmental influences on cellular and molecular ageing mechanisms is only just emerging. Indeed, there has been scepticism that early environmental influences could be detected in rates of ageing[23] and a call for integration of work in human populations with multidisciplinary studies of ageing in different model species subjected to nutritional and other challenges during preadult development. This approach has been taken in a series of studies by Ozanne and colleagues in Cambridge investigating the influences of an adverse early environment on a range of cellular and molecular ageing processes.[24] Using a rodent model of maternal protein restriction, they demonstrated that in the offspring, longevity can be influenced by early growth patterns and that underlying this may be changes in insulin metabolism, expression of antioxidant defence systems and levels of oxidative damage (including telomere attrition).

Another study showed that a murine model of a human syndrome linked to defective DNA repair resulted in animals with premature ageing but that the accumulation of DNA damage was restricted mainly to the embryonic period. This might be compatible with the high initial damage load hypothesis, which proposes that early development of living organisms produces an exceptionally high load of initial damage, comparable to the amount of subsequent ageing-related deterioration accumulated during the rest of life.[25] This hypothesis predicts that even small progress in optimizing early developmental processes could potentially result in major benefits in terms of slower ageing, prevention or postponement of age-related diseases and extension of healthy lifespan. Others have sought to summarize the evidence that telomere attrition might underlie the developmental origins of cardiovascular

disease in human ageing and found that most published studies to date were based on *in vitro* experiments or on tissue specimens collected at a single age so that individual variation in the rate of telomere attrition and how this might relate to growth rate and the rate of decline in vascular endothelial and metabolic function in individuals remain unknown.

Developmental influences on cellular and molecular ageing in muscle and bone

Muscle fibre number is a critical determinant of muscle mass and strength at all stages of life. It appears that fibre number is set at 24 weeks of human gestation and fibres are incapable of replication thereafter. Hence subsequent growth, maintenance and repair are believed to occur through muscle fibre hypertrophy rather than hyperplasia achieved by recruitment of myoblasts, derived from embryonic stem cells, at approximately 6 weeks of gestation in the human embryo. These observations suggest that key periods during gestation may influence the formation of myofibres and recruitment of myoblasts with long-term consequences for muscle mass and strength. The neonatal period appears to be particularly important for muscle growth through fibre hypertrophy.[26] Skeletal muscle is the fastest growing protein mass in neonates due to accelerated rates of protein synthesis accompanied by the rapid accumulation of muscle nuclei. Feeding profoundly stimulates muscle protein synthesis in neonates and the response decreases with age. The feeding-induced stimulation of muscle protein synthesis is modulated by enhanced sensitivity to the postprandial rise in insulin and amino acids. This capacity is further supported by enhanced myoblast proliferation, but how these two processes are linked remains to be established.

There is good evidence from animal models to support the concept of developmental plasticity of muscle. This is exploited in farming, where manipulation of the diet of livestock is routinely used to maximize muscle growth and therefore meat yield. Indeed, a recent study showed that peri-implantation and late-gestation maternal undernutrition differentially affected skeletal muscle development in fetal sheep.[27] There was evidence of reduced slow-twitch myofibre and capillary density in the fetal triceps but not the soleus with undernutrition at both time points. This reduction in fibre density, which may have been a consequence of decreased capillary density, was associated with higher insulin receptor, GLUT-4 and type 1 insulin-like growth factor receptor mRNA levels, suggesting a redistribution of resources at the expense of specific peripheral tissues as a consequence of undernutrition. Furthermore, there is evidence that the changes in insulin signalling due to *in utero* growth restriction may go on to result in altered trajectories of postnatal growth. Other studies involving experimental manipulation of early nutrition have similarly shown that prenatal maternal diet restriction is associated with reduced neonatal muscle weight in a range of mammalian models. In particular, maternal undernutrition appears to have a predominant effect on the growth and development of secondary fibres whereas the major influence on primary fibre number appears to be genetic, and there is evidence that these effects on muscle persist.[28]

Successful prenatal development depends on nutritional supply, utilization and hormonal regulation, and the maternal somatotropic axis plays a significant role in the control of myogenesis. For example, the infusion of growth hormone into pregnant sows up until mid-gestation results in overall increases in both birth weight and fibre numbers in the smallest littermates. This suggests an important role for cross-talk between nutrient availability, the growth hormone–insulin-like growth factor (GH–IGF) axis and regulation of fibre number with long-term consequences for muscle form, function and ageing in later life. These investigations have been taken further using the spontaneous differential fetal growth of pigs to investigate the mechanisms underpinning the link between fetal size and muscle development. The development of the longissimus muscle in small fetuses and their average-sized littermates was investigated on days 45, 65 and 100 of gestation, where term was 113–116 days. Small fetuses were reported to have significantly lower body weight at all time points and significantly reduced secondary to primary muscle fibre ratios on day 100 compared with littermates. The expression of the IGF-1 receptor and IGF binding protein (IGFBP)-3 were significantly higher at day 65 in the longissimus muscle of the small compared with the average-sized fetuses. IGF-1 receptor expression remained elevated at day 100 and was accompanied by significantly increased expression of the IGF-2 receptor and of IGFBP-5. These data suggest that reduced fetal muscle development is associated with increased expression of several genes of the IGF system in mid to late gestation, which may be compensatory to poor growth.[29]

The GH–IGF axis remains very important in neonatal growth and development and a study in rodents found that muscle from small neonatal rats secreted significantly more IGFBPs and less IGF than average-sized littermates. This differential expression, if maintained postnatally, could account for the persistence of small muscle size throughout life and have consequences for lifelong muscle function. Animal models have further demonstrated that efficiency of nutrient utilization is reduced in neonates, with intrauterine growth restriction suggesting altered function of the major organs involved in the digestion, absorption and metabolism of dietary nutrients. For example, proteomic analyses of the gastrocnemeus from small and normal weight newborn piglets demonstrated major adaptations in 13 proteins which were associated with reduced muscle size

at birth. These proteins related primarily to macronutrient metabolism, particularly protein synthesis and degradation, antioxidant function and immune response, and also to cellular structure. The postnatal consequences of reduced birth weight in lambs include slowed postnatal engagement of the GH–IGF system. When small lambs are reared in an optimum environment, they grow at rates comparable to average-weight lambs. However, they lay down more fat as a consequence of high energy intakes, low maintenance requirements and limited capacity for muscle and bone growth.

Akt is a protein kinase essential for metabolism and survival which acts downstream of both the IGF-1 and insulin receptors. Signalling through Akt, following the binding of IGF-1 to its receptor, is associated positively with muscle protein synthesis. Myofibre contraction has also recently been demonstrated to stimulate Akt signalling and GLUT4 translocation, both central regulators of glucose homeostasis. Among the intracellular mechanisms controlling protein synthesis, signalling via Akt appears to regulate gene transcription through inactivation of Forkhead box Os (FOXOs), which are associated with E3 ubiquitin ligase expression. mTOR is another important protein kinase. It regulates translation and its expression increases with increase in muscle hypertrophy and vice versa, suggesting an important role in determining muscle mass. Nutrition, insulin and IGF-1 all activate the Akt/mTOR pathway and it could therefore be postulated that older adults who had reduced birth weight and then developed insulin resistance in later life might have reduced mTOR concentrations or down-regulation of its activation.

Sirtuins may also be important. There is evidence that SIRT1 is central to the ability of adult skeletal muscle fibres to sense and react to nutrient availability, and it has been postulated that sirtuin expression might also be affected by nutrient restriction *in utero* or early childhood.

Studies identifying mechanisms for developmental influences on bone have also utilized animal models. A study of rats demonstrated that the experience of a low protein diet in prenatal life was associated with subsequent reduction in bone area and bone mineral content and also alteration in growth plate morphology in adulthood. There was also evidence of down-regulation of proliferation and differentiation of bone marrow stromal cells as assessed by fibroblast colony formation at 4 and 8 weeks. Subsequent work considered the effect of early undernutrition on the osteogenic environment and demonstrated changes in IGF-1, osteocalcin and vitamin D levels associated with alteration in skeletal structure which persisted into late adulthood.

There has been less work linking early environmental influences with changes in human muscle or bone at a molecular or cellular level. One small study involving 27 adult women looked at the relationship between size at birth and skeletal muscle morphology but did not find significant associations. In contrast, a more recent study focused on a group of 40 young men and showed that those with low birth weight had altered skeletal muscle fibre composition and also specific changes in muscle insulin-signalling protein expression. Most recently, the same group investigated mitochondrial function in the skeletal muscle of young men born with low birth weight and abnormal glucose metabolism in adult life. However they did not demonstrate underlying mitochondrial dysfunction. This cellular and molecular work now needs to be taken forward in studies of older adults to investigate mechanisms underlying the developmental origins of sarcopenia and osteoporosis. Of course, one of the main challenges is collecting tissue to carry out this type of basic science research, but interestingly a recent study demonstrated that it was both feasible and acceptable to carry out muscle biopsy in older men already taking part in an established epidemiological study.[30]

A life course approach to ageing and its relevance to clinical practice

Most research into human ageing focuses on influences operating in later life. However, there is considerable unexplained variation in markers of ageing and age-related disease between individuals of a similar age. A life course approach to ageing suggests that this is partly explained by the fact that manifestation of ageing in later life reflects not only the rate of decline experienced at that stage but also the peak attained earlier in life. This is illustrated with regard to musculoskeletal ageing in Figure 8.5. Thus the determinants of peak structure and function attained in early adulthood become an important focus, in particular influences on early growth and development. Understanding the role of developmental influences in ageing is relevant

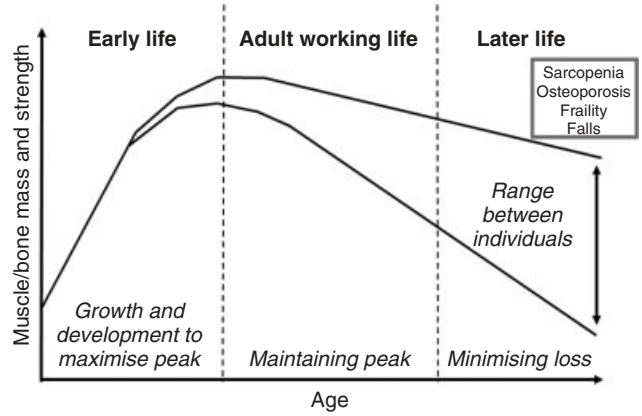

Figure 8.5 A life course approach to musculoskeletal ageing.

to clinical practice for several reasons. For example, it provides an opportunity to identify individuals at risk of accelerated ageing earlier in the life course. It also suggests that the window for instituting beneficial interventions should be widened to include all stages of life. Furthermore, knowledge of underlying mechanisms, particularly at the cellular and molecular level, has the potential to inform the development of novel therapeutic agents to minimize the detrimental effects of ageing.

Key points

- There is increasing recognition that developmental influences are relevant to human ageing.
- Small size at birth has been associated with increased mortality and morbidity from a number of age-related conditions, including cardiovascular disease, type 2 diabetes, sarcopenia and osteoporosis.
- Understanding the role of developmental influences in ageing has clinical relevance in terms of predicting accelerated ageing, widening the window for interventions and informing the development of novel therapeutic agents.

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CHAPTER 9

Sexuality and ageing

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Introduction

Sexuality remains an important component of quality of life throughout the lifespan. Sexuality is much more than the physical act of sex and encompasses intimate feelings, sensuality and the way we view ourselves or others see us as men and women. Relationships are influenced by sexuality and cultural codes of behaviour set the boundaries of what is considered to be acceptable or unacceptable behaviours in given contexts such as a nursing home. Myths and prejudice abound in terms of societal and professional expectations about the sexual activity and behaviours of older people and their needs in this area can easily be over looked. Cultural norms and values are changing and it is likely that future generations of older people will be more assertive in terms of seeking health care advice and interventions. However, it is important to recognize that current prejudices and myths about celibacy dominate western views of sexuality and sexual activity in later life, and this may inhibit older people from seeking help with sexual performance, sexual health and relationships.

The spectrum of sexuality and ageing is outlined in Table 9.1. The full expression of sexuality is dependent on biological, psychological and social factors. Testosterone is a driver of sexuality in both sexes, but its effect is modulated by psychological and social factors. The effects of ageing on sexuality can create major anxiety but, with adequate education, sexuality can remain enjoyable throughout life. There is much misinformation about sexuality. Although open discussion of sexuality has become much more common in the last 40 years, many older persons come from a generation where sexuality remains a taboo subject. This chapter explores both the biology of sexuality and ageing, and also the emergence of the special needs of a substantial cohort of older gays and their unique needs. The role of disease in the sexuality of older persons is addressed and, finally, the problems faced by older persons who have had lifelong paraphilias are considered.

In the United States, a survey of males and females aged 57–85 years found that 73% of persons 57–64 years of age were sexually active.[1] This prevalence declined to 26% of persons 75–85 years of age. Women at all ages were less sexually active than men. Sexual problems existed in half of the population but only 38% of men and 22% of women had discussed their sexual problems with a physician. Women reported a low desire (43%), poor vaginal lubrication (39%) and failure to climax (37%) as their main problems. About 37% of men had erectile dysfunction. Of these men, only 14% had used medications to improve their function. In a study of persons 75–85 years of age, 38.9% of men and 16.8% of women were sexually active.[2] Good health was the major factor predicting a healthy sex life.

Sexual health

It is essential that older people are informed and equipped to enjoy sexual activity safely. Older people are increasingly at risk at of sexually transmitted disease and they tend to delay seeking help longer than younger people from the onset of symptoms.[3] Access to age-sensitive information and health promotion is important; sexually transmitted diseases are not a prerogative of the young. It is important for health professionals to recognize that many of the older people who consult with them today have not benefited from health education programmes and may be unaware of the protection provided by condoms.[4]

Sexuality and the older woman

Many women associate menstruation with femininity, fertility and youth, which is in sharp contrast to the symbolism of menopause, which signals biological ageing triggering a new dynamic in self identity and sexuality. In the medical literature, the view that menopause is a deficient state is prolific, which some would argue is a social construction

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 9.1 Sexuality and ageing – the spectrum.

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

of ageing based on the medicalization of menopause and failure to recognize this as a natural life transition.[5] These debates aside, menopause is an individual experience derived from the interplay of physiological, psychological and other factors. Natural menopause occurs in women with an average age of 52 years. Epidemiological studies have suggested that the older a woman is at menopause, the longer she will survive following menopause. Smoking is a major cause of an early menopause.

Numerous studies of ageing and menopausal transition demonstrate multiple health-related changes, alterations to sexual response and impacts on intimate relationships that may lead a woman to seek support through either traditional or alternative medicine.[6] The major symptoms of menopause are hot flushes and night sweats. These occur in approximately 85% of women at the time of menopause. Although in most women hot flushes last less than 5 years, a few women continue to have them into their 80s. Environmental factors such as spicy foods, alcohol, caffeine and hot weather and psychological factors, for example, stress, can be precipitants of hot flushes. Hormone replacement therapy is commonly prescribed to treat menopausal symptoms and to prevent post-menopausal bone loss. A concern of some women is that such treatment will result in weight gain; as shown by a recent systematic review of 28 randomized controlled trials with 28 559 women, there is no evidence of an effect of unopposed estrogen or combined estrogen with progestogen on body weight.[7] It seems that body mass index increase is normal and associated with the onset of menopause that can be addressed by changes in life style, including diet and exercise. There is currently insufficient evidence to determine the role of exercise in the management of vasomotor menopausal symptoms.[8] Menopause is not necessarily associated with a decline in libido. Some women find the cessation of menses liberating. Use of estrogen is declining following the results of the Women's Health Initiative and the HERS study. These studies showed that both estrogen alone and estrogen plus progesterone were associated with an increase in myocardial infarction, stroke, pulmonary embolism and breast cancer.[9,10] This was balanced by a decrease in hip fracture and colon cancer. Unfortunately, estrogen also appears to accelerate the onset of cognitive impairment in older women.[11]

Testosterone levels decline rapidly between the ages of 20–40 years in women.[12] There is then a slight increase in testosterone levels in women between the ages of 60 and 80 years. Testosterone, tibolone (an estrogen–progestagen–testosterone) and dehydroepiandrosterone (DHEA) all improve libido in older women. In addition to increasing libido, testosterone has also been reported to improve general well-being, decrease mastalgia, decrease headaches and increase bone mineral density and muscle mass (Table 9.2). The testosterone products available for women are listed in Table 9.3. A number of studies have shown positive effects of testosterone patches in women with female sexual desire disorder.[13]

Female hypoactive sexual desire disorder is defined as persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. This must cause marked distress or interpersonal difficulty. The condition cannot be better ascribed to another psychiatric condition, for example, depression or to the effects of a substance, for

Table 9.2 Testosterone and women.

↑ Libido
↑ General well being
↓ Mastalgia
↓ Headaches
↑ Bone mineral density
↑ Muscle mass

Table 9.3 Testosterone products available for older women.

Testosterone
Compounded vaginal creams
Gels
Testosterone undecanoate
Estratest (estrogen plus methyltestosterone)
Tibolone
Dehydroepiandrosterone
Testosterone patch, testosterone pellets

Table 9.4 Management of sexual dysfunction in older women.

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

example, medication or a general medical condition. The approach to the management of sexual dysfunction in older women is given in Table 9.4.

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

The major sexual problems reported by older women include lack of orgasm, lack of sexual interest, a decline in lubrication, failure to find an appropriate partner, dyspareunia, problems with safe sex and sexual intercourse decline from 30–78% at 60–70 years to 8–43% at 80 years. Most older persons who are still sexually active have intercourse an average of once per week. Approximately 45% of older women masturbate. Of those still having intercourse, 73% enjoy intercourse and the rest tolerate it. Only 21% of women over the age of 75 years still have a partner. Most studies have shown that the majority of physicians do not include sexual concerns and questions as part of their general history taking. Figure 9.1 provides the spectrum of sexuality and the older female.

A number of diseases have a major impact on sexuality in women. The disease that most alters a woman's self-image is breast cancer. Up to 40% of women with breast cancer have a reduction in their sexual activity.[14] The effect of breast cancer on sexuality is highly dependent on the relationship that the woman has with her partner. Urinary incontinence can modify sexual interactions in up to one-third of women. Severe incontinence may lead to the need for separate beds. Uterine prolapse is more likely than incontinence to alter sexual relationships. Urogenital atrophy, due to estrogen deficiency, leads to vaginal dryness, vaginal bleeding, urge incontinence, urinary frequency and dysuria, irritation and pruritus of the labia and mons, dyspareunia and urinary tract infections. All of these changes can lead to sexual dysfunction. A number of lubricants are now available to allow women to overcome vaginal dryness. Estrogen creams, tablets and rings

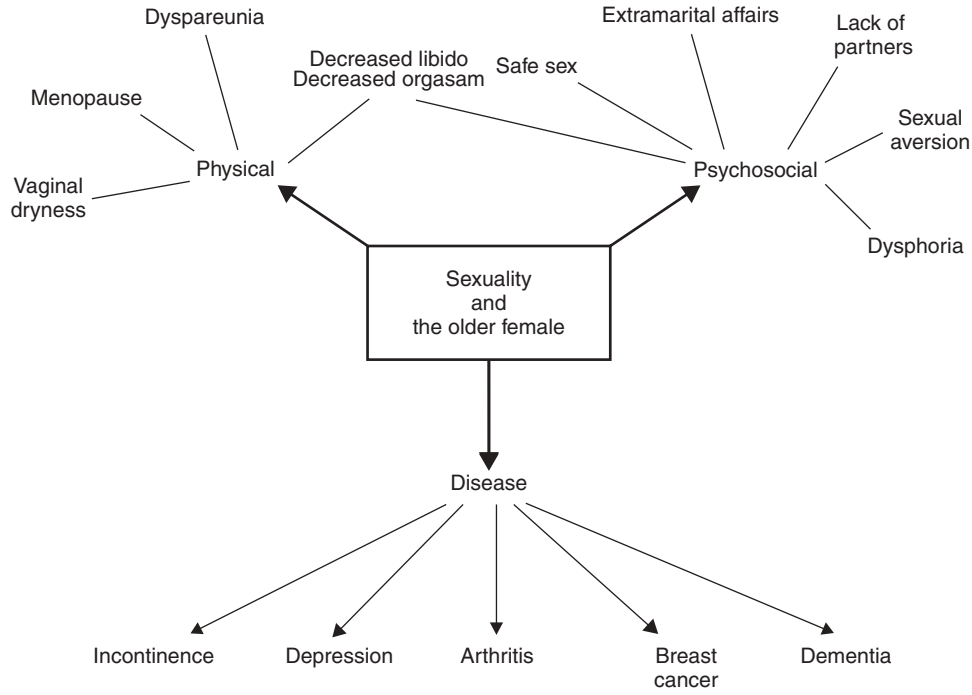

Figure 9.1 Sexuality and the older female.

may also be useful in the management of severe vaginal dryness. However, it must be remembered that vaginal estrogen is absorbed and may have all the effects of oral or parenteral estrogen.

Erectile dysfunction

Erectile dysfunction is defined as the inability to attain or maintain a penile erection sufficient for sexual performance on at least two-thirds of occasions.[15] Physiologically, older males have an increased time for development of erection and less full erections with a decreased pre-ejaculatory secretion. During orgasm, there is a decline in expulsive force and urethral contractions. Following ejaculation, there is a rapid tumescence with rapid testicular descent. The refractory period is markedly prolonged.

A number of older males have an active sex life.[16] However, studies in Germany and South America has found that 53% of men aged 70–80 years have some degree of erectile dysfunction.[17] The Massachusetts Male Aging Study showed that at 40 years of age, severe erectile dysfunction was present in 5.1% and moderate erectile dysfunction in 17%.[18] By the age of 70 years, 15% had severe dysfunction and 34% moderate dysfunction. In the Olmsted County Study, 30% of men over 70 years of age had no erections and only 10% had intercourse more than once per week.[19] The major risk factors for developing erectile dysfunction are heart disease, diabetes mellitus and hypertension.

Erections occur when the smooth muscle of the corpora cavernosa relaxes, allowing pooling of blood. Figure 9.2 demonstrates the different neurotransmitters involved in producing penile erection.

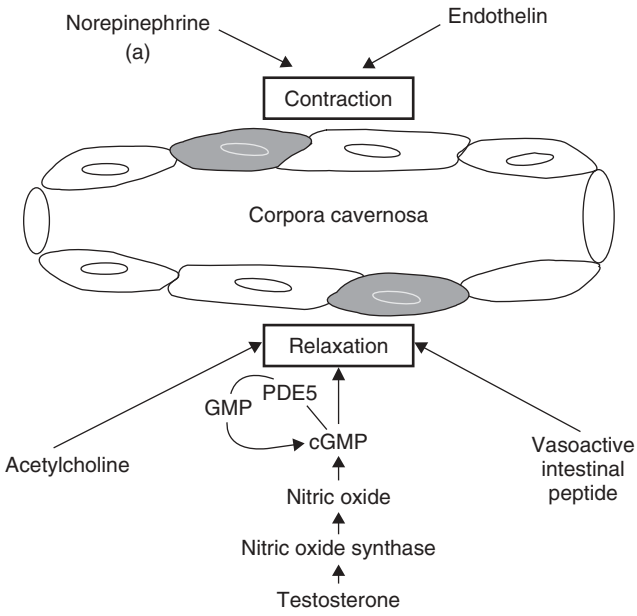

Figure 9.2 Neurotransmitters involved in producing a penile erection.

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

While low testosterone levels decrease the production of nitric oxide synthase, most studies have failed to show that hypogonadism is a major cause of erectile dysfunction.[20] Nevertheless, persons with low testosterone have poor-quality erections. Testosterone treatment improves the quality of erections produced by phosphodiesterase-5 inhibitors.

Table 9.5 lists the causes of erectile dysfunction and Table 9.6 lists the available management strategies for it.

The most common treatment for erectile dysfunction is a phosphodiesterase-5 inhibitor. This works by blocking the breakdown of cyclic GMP that has been generated by nitric oxide. There are three phosphodiesterase inhibitors in general use: sildenafil, vardenafil and tadalafil. The pharmacokinetics of these drugs is given in Table 9.7. The major side effects of phosphodiesterase-5 inhibitors are headache, flushing, dyspepsia, rhinitis, visual disturbances, hypotension and death (Table 9.8). Persons on nitrates and α-adrenergic blockers should avoid phosphodiesterase-5 inhibitors. With ageing, all phosphodiesterase-5 inhibitors

Table 9.5 Causes of erectile dysfunction.

Vascular
Atherosclerosis
Vascular leak
Medications
Neurological
Peripheral neuropathy
Spinal cord disease
Temporal lobe epilepsy
Urological
Endocrine
Diabetes mellitus
Hypothyroidism
Hyperthyroidism
Hyperprolactinaemia
Peyronie's disease
Recreational drugs
Tobacco
Alcohol
Opiates

Table 9.6 Treatment options for an older male with erectile dysfunction.

Psychological
Drugs
Sildenafil/vardenafil
Uprima (apomorphine SR)
Phentolamine
Intracavernosal injections
Alprostadil
Papaverine
Phentolamine
Vacuum tumescence device
Penile prosthesis

Table 9.7 Pharmacokinetics of the phosphodiesterase-5 inhibitors.

Parameter	Sildenafil	Vardenafil	Tadalafil
T_{Cmax} (h)	1	1	2
$T_{1/2}$ (h)	4	4–6	17.5

Table 9.8 Side effects of phosphodiesterase-5 inhibitors'.

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

have increased plasma concentration or area under the curve.

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

A number of complementary medicines claim to improve erections, such as cantharidin and ginsenosides. These do not work and can produce haematuria.

Overall, modern medicine will allow the majority of older males to obtain an erection (Table 9.6). It is important to include the partner in decisions concerning which approach is best. It is important not to assume that an older male's partner is his spouse.

Andropause

It is now recognized that testosterone levels decline at the rate of 1% per year.[21] This decline leads to 3–5% of persons 40–50 years of age and 30–50% of persons over 70 years of age having biochemical hypogonadism. Other estimates suggest that 20% of persons 40–70 years of age are hypogonadal. When testosterone levels fall below the normal level for men 20–40 years of age and this is accompanied by symptoms such as a decline in libido or fatigue, the person is recognized as having andropause or androgen deficiency in ageing males (ADAM). Other terms that have been used historically, for example, climacteric or male menopause, are no longer considered acceptable. Two symptom-screening tests have been developed to screen for males with andropause. These are the ageing male symptom (AMS) and the ADAM questionnaires[22] (Tables 9.9 and 9.10). Both have excellent ability to detect males with biochemical hypogonadism but also are answered positively by a large number of males who are not hypogonadal, for example, older persons with depression.

The cause of the fall in testosterone with ageing is multifactorial (Table 9.11). Although levels of luteinizing hormone are slightly higher in hypogonadal older males, it is rarely out of the normal range. Hence these males are considered to have secondary (hypothalamic–pituitary) hypogonadism. The major cause of this seems to be irregular (chaotic) secretion of gonadotrophin-releasing hormone from the hypothalamus. There is also an increase in negative feedback of testosterone at the pituitary level. A decline in testosterone response to human chorionic gonadotrophin is present in older men. There is a decrease in Leydig cell number.

With ageing, there is an increase in sex hormone-binding globulin (SHBG). This leads to less testosterone being available to the tissues. Therefore, the tissue-available testosterone can either be measured directly using a free testosterone value by dialysis or a bioavailable testosterone (ammonium sulfate precipitation technique). Alternatively, tissue-available testosterone can be calculated using an SHBG, total testosterone and albumin by utilizing the

Table 9.9 ADAM questionnaire[a].

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

[a]A positive answer represents yes to 1 or 7 or any three other questions (circle one).

Table 9.10 AMS questionnaire. Which of the following symptoms apply to you at this time? Please mark the appropriate box for each symptom. For symptoms that do not apply, please mark 'None'.

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

program available at www.issam.ch. Most experts feel that some measure of tissue-available testosterone is preferable to measuring a total testosterone in making the diagnosis of andropause.[12]

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

The symptomatic concept of andropause has been recognized since the time of the Chinese Text of Internal Medicine. The major symptom of andropause is a decline in libido. A decline in libido may also be due to depression, illness or death of a spouse. Testosterone replacement restores libido in 70–80% of persons. Testosterone is also essential for the production of nitric oxide synthase. Production of nitric oxide is essential for firmness of the erection.

Table 9.11 Age-related changes in testosterone regulation.

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

Table 9.12 Effects of testosterone in older males.

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

Thus, low testosterone levels can lead to soft erections or failure of phosphodiesterase-5 inhibitors to produce an erection. Low testosterone levels are associated with a low ejaculatory volume.

The effects of testosterone in older males are listed in Table 9.12. Testosterone increases muscle mass and strength. Testosterone stimulates the stem cells to produce satellite cells (these are responsible for repair of skeletal muscle) and also increase protein synthesis in skeletal muscle and inhibit the ubiquitin–proteasome system, which is responsible for muscle breakdown. Testosterone inhibits adipocyte precursor cells, resulting in a loss of fat mass. Testosterone may improve function, but at present there are limited data in this regard. Testosterone increases bone mineral density in the lumbar spine and the hip, improves visuospatial cognition and increases the haematocrit. Testosterone may have beneficial effects on the cardiovascular system. Testosterone's negative effects include gynaecomastia, water retention and possibly sleep apnea. The effects of testosterone on the prostate are uncertain. Testosterone cannot be given to persons with active prostate cancer.

The history of testosterone replacement stretches from the end of the nineteenth century when Brown-Sequard injected himself with an animal extract of testosterone. During the early twentieth century, 'monkey gland', goat testicle and even human testicular transplants were done on the rich in an attempt to rejuvenate them. The available and experimental forms of modern testosterone replacement are listed in Table 9.13. At present, most men with andropause choose to use the testosterone gel forms of treatment. After the gel, the next most popular form of treatment is testosterone injections. Selective androgen receptor molecules (SARMs) have been developed to avoid the sexual stimulant properties of testosterone and enhance the anabolic features of testosterone replacement. These can be steroids, for example, nandrolone or oxandrolone, or a series of non-steroid molecules that can be ingested orally.

Table 9.13 Testosterone therapies and the older male.

Injections
Patches
Gel
Oral
Inhalation
Pellets
Buccal/sublingual
Nasal

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

Sexuality and disease

Disease can greatly alter the sexuality of an individual. Pain and disability can interfere with sexual intercourse. Fatigue reduces libido. Negative self-image is commonly associated with diseases. Depression, with or without other systemic diseases, can lead to a decline in libido or erectile function. Many systemic diseases reduce testosterone, leading to a decrease in libido.[23]

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

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

Persons with left cerebrovascular hemisphere strokes have a marked decrease in libido. Coital frequency is markedly decreased in two-thirds of persons following a stroke. Persons with a stroke can often have hemineglect and their partners need to be aware of this problem.

Table 9.14 Instructions for patients and their spouses after myocardial infarction.

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

Sexual activity can be restored in male patients with normal pressure hydrocephalus after shunt placement.[24] Men and women with Parkinson's disease have a high prevalence of sexual dysfunction. Very low testosterone levels have been reported in men with Parkinson's disease. Pelvic organ prolapse when severe is associated with a decrease in sexual activity.[25]

Death during sexual intercourse in persons with cardiovascular disease is extremely rare, with an estimated rate of 0.2 per 100 000 being reported in males.[26] Cardiovascular disease and hypertension are major risk factors for erectile dysfunction. Persons with two- or three-vessel disease have softer erections and more erectile dysfunctions than those with one-vessel disease. In females, heart disease is associated with decreased libido, vaginal dryness, dyspareunia, orgasmic difficulty and decreased genital sensation. Saint Louis University has developed a series of instructions for patients for resuming coitus following myocardial infarction (Table 9.14).

The older homosexual

There are approximately 3 million older gays in the United States. It is estimated that approximately 4% of older women are lesbian and/or bisexual. Older gays tend to have a higher use of alcohol and tobacco. The Women's Health Initiative found a slightly greater rate of obesity and dysphoria in older lesbians.[27] Breast cancer was more common in lesbians.

Nearly one-quarter of AIDS cases in developed nations occur in persons over the age of 65 years.[28] By 2015, 50% of HIV-infected males in the United States will be over 50 years of age. The rate of CD4+ all cell loss is more rapid in older males. Older persons are less likely to be screened for HIV. There has been a marked increase in males over 50 years of age looking for sex on the Internet.[29] Condom use is extremely rare in gays over 50 years of age. HIV testing is rare in older gays.

Homophobia leads to many older gays not identifying themselves to health care providers. Many physicians assume that their older patients are heterosexual. Unmarried homosexual partners are often poor as they grow old as they are ineligible, in the United States, for social benefits such as Social Security. A major issue occurs when the partner becomes sick, as the homosexual partner often has no rights to make health care decisions for their ill partner. It is important that older gays have a durable power of attorney for health, designating their partner as the decision-maker. There are numerous unmet health and social service needs of gay and lesbian elders.[30]

Paraphilias

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

Paedophilia is sexual abuse of a child by an adult. In one series of 261 cases, the child abuser was the grandfather in 16 cases.[31] Paedophilia needs to be reported to the appropriate authorities.

Sexuality in the nursing home

Sexuality does not necessarily cease on entry into a nursing home. However, within the nursing home there are multiple barriers to sexuality.[32] These include lack of privacy,

lack of a partner, staff and resident attitude and knowledge concerning sexuality and family attitudes. Special ethical problems arise when two demented patients form a romantic liaison. Most ethicists feel that older persons should retain their right to continue appropriate sexual behaviour in the nursing home. It has been suggested that older persons may wish to develop an advanced directive for sexual behaviour.

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

Sexual disinhibition is not uncommon, with a prevalence of about 2% in the community and as high as 25% in nursing homes.[33] No randomized control trials exist for the pharmacological treatment of sexual aggression. The use of behavioural management whenever possible is recommended. Use of antiandrogens and estrogens in males is associated with an increase in side effects and therefore cannot be recommended.

Conclusion

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

Key points

- Sexuality is important throughout the lifespan.
- Erectile dysfunction is the major problem in older males.
- In older women, the major problems are reduced libido, poor lubrication and failure to climax.
- There are biological, psychological and social components of sexuality.
- Alternative sexual lifestyles are not unusual in older persons.

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CHAPTER 10

Physical fitness and exercise

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Introduction

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

What is exercise?

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

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

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

Dose–response relationships between changes in fitness and better health outcomes have been defined for some, but certainly not for all, diseases and syndromes. Some modalities or doses of exercise that are promoted for older

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

Does exercise increase life expectancy?

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

Preserving exercise capacity with age via an active lifestyle

There is a great similarity between the physiological changes attributable to disuse and those which have been typically observed in ageing populations, leading to the speculation that the way in which we age may be modulated with attention to activity levels.[1] The most important physiological changes associated with ageing or disuse that impact upon exercise capacity are presented in Tables 10.1–10.4. In most physiological systems, the normal

Table 10.1 Changes in exercise capacity due to ageing or disuse potentially modifiable by physical activity.

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

Table 10.2 Changes in cardiorespiratory function due to ageing or disuse potentially modifiable by physical activity.

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

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

Table 10.3 Changes in metabolism and body composition due to ageing or disuse potentially modifiable by physical activity.

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

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

Table 10.4 Changes in central and peripheral nervous system due to ageing or disuse potentially modifiable by physical activity.

Function	Effect of ageing or disuse
REM[a]and slow-wave sleep duration	Decrease
Cognitive processing speed, accuracy	Decrease, no change
Attention span	Decrease, no change
Memory	No change, decrease
Executive function	Decrease, no change
Motor coordination, force control	Decrease
Neural reaction time, neural recruitment	Decrease
Autonomic nervous system function	Decrease

[a]REM, rapid eye movement.

ageing processes do not result in significant impairment or dysfunction in the absence of pathology and under resting conditions. However, in response to a stress or significant disuse, the age-related reduction in physiological reserves ('homeostenosis') may result in difficulty in completing a task requiring near-maximum effort.

Although changes in maximum work capacity (aerobic fitness or maximum oxygen consumption) will be immediately noticeable and disastrous for an elite athlete, they may accrue insidiously in non-athletic populations because most sedentary individuals rarely call upon themselves to exert maximum effort in daily life. Women are particularly susceptible here, because their initial reserve of muscle mass is so much lower than that of men, owing to gender differences in anabolic hormonal milieu and also lifestyle/occupational factors. They will therefore cross this threshold where losses of musculoskeletal capacity impact on functional status at least 10 years before men do on average.

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

Many studies suggest that chronic adaptation to physical activity can markedly attenuate decrements in exercise capacity that would otherwise occur with ageing (see Tables 10.1–10.4), with the notable exception of maximum heart rate (due to declining sensitivity to β-adrenergic stimulation in the ageing heart).[2] Although the peak exercise workload achievable is therefore always lower in aged individuals, the cardiovascular and musculoskeletal adaptations to chronic aerobic exercise enable the trained individual to sustain higher submaximum workloads with less of a cardiorespiratory response (heart rate, blood pressure and dyspnoea), and also less overall and musculoskeletal fatigue.

Musculoskeletal function (strength, power, muscle endurance) in ageing is dictated largely by the size of the muscle mass which is contracting and to a lesser extent by changes in surrounding connective tissue in the joint (cartilage, tendons and ligaments) and neural recruitment, conduction velocities, glycolytic and oxidative enzyme capacities and fatigue patterns. Sedentary individuals lose large amounts of muscle mass over the course of adult life (20–40%) and this process, termed *sarcopenia*, plays a major role in the similarly large losses in muscle strength observed in both cross-sectional and longitudinal studies.[3] However, unlike many other changes which impact on exercise capacity, muscle mass cannot usually be maintained into old age even with regular aerobic

activities in either general populations or master athletes. Only overloading of muscle with weight-lifting exercise (resistance training) has been shown largely to avert losses of muscle mass (and also strength) in older individuals. For example, Klitgaard *et al*.[4] found that elderly men who swam or ran had similar measures of muscle size, strength and metabolism as their sedentary peers, whereas the muscle of older men who had been weight-lifting for 12–17 years was almost indistinguishable, and even superior in some aspects, to that of healthy men 40–50 years younger than them.

Clearly, habitual exercise has the potential to lessen the impact of biological ageing on two of the major elements of exercise capacity: aerobic fitness and muscle strength. Similarly, there is evidence that balance training and flexibility training[5] induce adaptations in associated declines in these areas.

Optimization of body composition with ageing

'Usual ageing' is associated with significant losses of bone and muscle (lean mass) and increases in adipose tissue, along with central and visceral shifts in the regional distribution of adipose tissue stores. The extent to which these changes occur in an individual depends upon a combination of genetic-, lifestyle- and disease-related factors that are all interrelated. All of these body composition changes may impact negatively upon metabolic, cardiovascular and musculoskeletal function,[6] even in the absence of overt disease, and therefore it is important to anticipate them and optimize lifestyle choices and other treatments which can counteract the negative effects of ageing and/or disease on body composition. As detailed in the sections that follow and outlined in Table 10.5, one of the most potent pathways from physical activity to health status involves the modulation of these age-related shifts in body composition by habitual exercise patterns.

Role of exercise and physical activity in bone health and fracture risk

Age-related changes in bone

Bone mass begins to decrease well before the menopause in women (as early as the 20s in the femur of sedentary women) and accelerates in the perimenopausal years, with

Table 10.5 Exercise recommendations targeting optimal body composition for older adults.

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

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

continued declines into late old age. Similar patterns are seen in men, without the acceleration related to loss of ovarian function seen in women. As with losses of muscle tissue (sarcopenia), many genetic-, lifestyle-, nutritional- and disease- and medication-related factors enter into the prediction of bone density at a given age.

Physical activity and bone health

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

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

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

Consistent with bone density findings noted above, hip fracture incidence has been observed to be as much as 30–50% lower in older adults with a history of higher levels of physical activity in daily life, compared with age-matched, less active individuals. For example, in the prospective epidemiology of osteoporosis study (EPIDOS) study of 6901 white women over the age of 75 years followed for 3.6 years, investigators found that a low level of physical activity increased the risk for proximal humerus fracture by more than twofold. The relative risk of fracture in sedentary women (RR = 2.2) was greater than that attributable to low bone density (RR = 1.4), maternal history of hip fracture (RR = 1.8) or impaired balance (RR = 1.8). The interaction of these risk factors is indicated by the fracture rate, which rose from about 5 per 1000 woman-years in individuals with either bone fragility or high fall risk to 12 per 1000 woman-years for women with both types of risk factors. Such data suggest the great potential utility of multifactorial prevention programmes for osteoporotic fracture that can address both bone density and fall risk (sedentary behaviour, sarcopenia, muscle weakness, poor balance, polypharmacy, etc.) simultaneously.

Exercise intervention trials in postmenopausal women and older men

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

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

Optimal exercise modality and intensity for bone health

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

The relative efficacy of aerobic versus resistive exercise regimens for postmenopausal women may perhaps be best assessed via studies that have directly compared various intensities of these two exercise modalities in randomized subjects. Kohrt *et al*.[7] found that both aerobic activities with high ground-reaction forces (walking, jogging, stair climbing) and exercises with high joint-reaction forces (weight-lifting, rowing) significantly increased the BMD of the whole body, lumbar spine and Ward's triangle,

whereas only the ground-reaction group increased BMD at the femoral neck.[7] The weight-lifting group preserved femoral-neck BMD relative to controls, as has been seen in other resistance training studies. However, lean mass and muscle strength increased only in the weight-lifting group, leaving overall benefits of these two types of exercise for ultimate fall and fracture prevention still unresolved. Kerr *et al*.[8] randomized 126 postmenopausal women to 2 years of high-intensity weight-lifting exercise, moderate-intensity aerobic training (circuit training and stationary cycling) or sedentary control condition. Total hip and intertrochanteric BMD was improved only by strength training and was significantly different from aerobic training or control groups (+3.2% at 2 years). As most comparative studies other than those of Kohrt *et al*.[7] and Kerr *et al*.[8] have not sought to optimize both modalities, it is still not possible to choose definitively one best modality for all bone sites. In general, the older the individual, the more favourable the resistance training appears, due to its broader benefits on muscle, bone, balance and fall risk, relative to aerobic training. If aerobic training is chosen, however, activities that are weight bearing and higher impact have a greater efficacy than non-weight-bearing or low-impact aerobic activities.

It is important to consider not only the optimal modality of exercise, but also the relative intensity, as the skeletal adaptation is critically linked to the *intensity* of the loading (whether due to increased amount of weight lifted during resistance training or higher ground-reaction forces during aerobic/jumping activities). Interesting results have been reported by Cussler *et al*.[9] in a randomized trial of 140 postmenopausal women participating in a multimodal exercise programme (high-intensity resistance training and a weight-bearing circuit of moderate-impact activities including walking/jogging, skipping, hopping, stair climbing/stepping with weighted vests). Bone density improvements at the femoral trochanter were significantly and linearly related to total weight lifted during the 12 months, and also total weight lifted in leg press, squats and military press exercises, but not to volume or quality of the non-resistance training components of the programme. High-intensity resistance training is also more beneficial than low-intensity training for muscle strength gains and muscle hypertrophy, in addition to associated gait disorders, functional impairments and disability, making it ideal as a multiple risk factor intervention strategy for injurious falls in osteopenic women.

Exercise in the treatment of osteoporotic fracture

In older men and women who have already sustained an osteoporotic fracture, exercise is still extremely important to assist in recovery of function and also prevent recurrent injurious falls. Progressive resistance training has been shown to be superior to standard physical therapy during the recovery from hip fracture in elderly patients. In addition, resistance training has been shown to be a potent treatment for depression in the elderly and may thus be able to substitute for antidepressant medications, which are known to increase the risk of falls and hip fracture. A combination of resistance training and balance training may offer the best approach to rehabilitation in this setting, as it optimally targets several of the remediable physiological risk factors for falls, fractures and disability in this cohort. Additional studies are needed to define the effects of training in this clinical setting on bone density and strength itself, and also the optimal timing and duration of such interventions in the post-fracture recovery period.

Role of exercise and physical activity in adipose tissue accretion and distribution

The rising epidemic of obesity is now recognized internationally in both younger and older cohorts and is projected, if it continues, to lead to major changes in related diseases such as diabetes, and also life expectancy itself. Prevention of excess adiposity is both protective, and in some cases therapeutic, for many common chronic diseases, offering significant risk reduction in the case of osteoarthritis, cardiovascular disease, gall bladder disease, type 2 diabetes, breast, colon and endometrial cancer, hypertension, stroke and vascular impotence, for example. Although generalized obesity is associated with excess mortality, cardiovascular disease, osteoarthritis, mobility impairment and disability, it is predominantly excess visceral fat that is associated with the derangements of dyslipidaemia, elevated fibrinogen, hyperinsulinaemia, glucose intolerance or diabetes, vascular insulin resistance, hypertension and cardiovascular disease known as *metabolic syndrome* or *insulin resistance syndrome*. Reductions in visceral fat have been shown to improve glucose tolerance and insulin sensitivity in non-diabetic and type 2 diabetic subjects and changes in trunk fat correlate with improved glycaemic control in type 2 diabetics.[10] Hence the potential for exercise to impact favourably on the accretion and distribution of adipose tissue, as reviewed below, has enormous significance in that it may reduce the burden of disease expressed in the ageing population.

Cross-sectional studies of physical activity and fat mass

Numerous cross-sectional analyses have confirmed an inverse relationship between physical activity and abdominal fat. Master athletes compared with age- and BMI-matched controls have lower waist circumference and physically active women have lower waist-to-hip ratios than inactive women. It has been determined that the higher the intensity of activity independent of energy expenditure, the lower are the abdominal fat estimates for men and women. In a study of monozygotic and

dizygotic female twins, physical activity was the strongest predictor of central obesity after controlling for genetic and environmental factors and this persisted for those with a genetic predisposition to obesity.

Experimental studies of the influence of physical activity on abdominal fat

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

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

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

Relationship between exercise intensity and changes in body fat

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

Relationship between exercise modality and changes in body fat

There is no evidence that aerobic training is better than resistance training for reducing abdominal fat. Both resistance and aerobic exercise, at doses resulting in a sustained negative energy balance for several months, will generally result in significant reductions in fat mass when sensitive measurement techniques (generally not anthropometrics) are used. Resistance exercise may be more suitable as a fat reduction strategy for older obese individuals who have cardiovascular disease, arthritis, osteoporosis or mobility disorders, who may not tolerate moderate- to high-intensity aerobic training or who may need the added benefits of resistance training for maintenance of muscle and bone mass. Importantly, energy restriction results in significant losses of muscle and bone and the addition of resistance training to hypocaloric dieting has been shown to prevent such adverse body composition changes,[11] whereas aerobic exercise alone does not. Combined aerobic and resistance training has demonstrated a superior effect to aerobic training alone on trunk fat for older men. More well-designed studies are needed, particularly in overweight older adults, to explore the relative benefits of these modes of exercise for optimizing body composition.

Role of exercise in muscle mass preservation with age

An increase in muscle mass, in contrast to changes in fat and bone, is only achievable to a significant degree with progressive resistance training or generalized weight gain from extra energy and protein consumption and has a potential role in prevention of diabetes,[12] functional dependency and falls and fractures, in addition to being important in the treatment of chronic diseases and disabilities which are accompanied by disuse, catabolism and sarcopenia. For some diseases, such as type 2 diabetes mellitus, there are potential advantages to both minimizing fat tissue and maximizing muscle tissue, since these compartments have opposite and likely independent effects on insulin resistance in the elderly. Resistance exercise coupled with a leucine-enriched essential amino acid diet is recommended for the treatment of sarcopenia.[13] Muscle wasting or atrophy from any cause will exacerbate problems related to the extent and rate of the peripheral disposal of glucose into skeletal muscle, which is essential for maintenance of euglycaemia in response to normal metabolism, meals or other stressors. There is evidence from a variety of epidemiological and experimental studies that muscle weakness, decreased muscle mass, decreased activation of glycogen synthase and alterations in numbers of type IIb skeletal

muscle fibres are related to, and may precede, insulin resistance, glucose intolerance and type 2 diabetes expression. Thus, the typical alterations in body composition with ageing (decreased muscle mass and increased visceral adiposity) are potentially independently related to the development of impaired glucose homeostasis in older adults.

Exercise to maintain or increase muscle mass

Appropriate progressive resistance training programmes of 3–6 months' duration can be shown to increase muscle strength by an average of 40–150%, depending on the subject's characteristics and intensity of the programme and to increase total body lean mass by 1–3 kg or muscle fibre area by 10–30%.[14] Thus, even if some of the neural control of muscle and absolute number of motor units remaining is not affected by exercise, the adaptation to muscle loading, even in very old age,[15] causes neural, metabolic and structural changes in muscle which can compensate for the strength losses, and in some cases the atrophy, of ageing. Generally, strength gains after exercise far exceed, and are not directly correlated with, changes in muscle size, due to the importance of neural adaptation in this process.

Predictors of muscle hypertrophy after exercise

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

High-velocity resistance training

A relatively recent area of investigation is that of power training (high-velocity resistance training), which has been proposed as a better way to target the selective fast-twitch fibre atrophy characteristic of ageing muscle, and also the earlier and more precipitous decline in muscle power and its associated disability, relative to muscle strength in older men and particularly women. Power training has been shown to be effective in both healthy[16] and frail elders[17] and results in muscle hypertrophy, strength and power gains and improvements in balance and functional performance. Optimal training regimens for maximization of muscle power are still being defined.

Promotion of psychological well-being

Psychological well-being is vital to optimal ageing and is dependent on a host of factors, including genetic traits, social support systems, personality types and the presence of positive and negative psychological constructs such as happiness, optimism, morale, depression, anxiety, self-esteem, self-efficacy and vigour. Physical activity participation has been shown to be associated with more positive psychological attributes and a lower prevalence and incidence of depressive symptoms in cross-sectional and prospective epidemiological studies and experimental trials.[18,19] It is notable that effects are most significant in those with comorbid illness, such as cardiovascular or pulmonary disease or major depression,[18,20] attesting to the clinical relevance of this exercise adaptation.

The experimental evidence for exercise as an isolated intervention for the treatment of clinical depression in both younger and older cohorts is robust and consistent. Both aerobic and resistance training exercise produce clinically meaningful improvements in depression in such patients, with response rates ranging from 25 to 88%. In the studies that have addressed the issue of exercise modality, resistance training was found to be equivalent to aerobic training in young adults with depression and yoga as effective as aerobic exercise. Blumenthal *et al*. directly compared high-intensity aerobic exercise with antidepressant medications in older adults with major depression and found the two approaches to be equipotent, with no added benefit of combined exercise and medication.[20] Singh *et al*. compared high- and low-intensity progressive resistance training to GP referral and care in older adults with major depression and found that a clinical response (50% reduction in Hamilton Rating Scale for depression) was achieved in 61% of high-intensity training, 29% of low-intensity training and 21% of the GP care group.[19] Similarly, low-intensity aerobic training in older adults with depression has been shown to be similar in efficacy to social contact, reducing depression scores by only 30%. Thus, the literature on exercise and depression suggests that it is effective in young and old, it is approximately as effective as antidepressants in clinical cohorts, that both aerobic and resistance modalities appear equally beneficial and that optimal responses are seen with higher intensities of training.

Exercise and cognitive function

There is a growing body of observational data and experimental evidence that physical activity can exert significant influences on a wide range of cognitive functions.[21] The earliest lines of evidence were provided by cross-sectional studies of athletes or physically active individuals versus sedentary controls, with active or fit individuals demonstrating superior performance in tests of reaction

time, motor control and visual–spatial tasks. Changes in executive-control processes and also changes in brain structures and functions most closely related to these processes are disproportionately affected by ageing and exercise in some studies.[21,22] This has led to speculation that age-related cognitive dysfunction might be partially mediated by suboptimal and diminishing participation in physical activity across the lifespan. Virtually all of these studies have focused on cardiorespiratory fitness (maximum oxygen consumption) or aerobic exercise as the putative protective factor. However, ~50% of the variance in maximum oxygen consumption in children and adults is thought to be mediated by genetic factors rather than physical activity patterns,[23] raising the possibility that shared predisposition to low fitness, vascular risk factors and cognitive decline may explain these associations, rather than adaptation to an active lifestyle. In addition, changes in maximum oxygen consumption with ageing are explained as much by losses of muscle mass (sarcopenia) as they are by losses of cardiovascular reserve, suggesting that non-aerobic activities could be just as important as aerobic activities for the prevention of cognitive decline.

More recently, well-designed prospective cohort studies that have controlled for many known risk factors for cognitive dysfunction have in large part supported cross-sectional associations between physical activity patterns and risk of dementia.[24] For example, in the Honolulu–Asia Aging Study,[25] 2257 physically capable, cognitively intact men aged 71–93 years were followed for 7 years for incident dementia. Walking significantly reduced the risk of dementia in a dose-dependent fashion, with a 1.8-fold increased risk for those who walked less than 0.25 miles per day compared with >2 miles per day, controlling for other possible risk factors.

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

A recent meta-analysis found that physical exercise protected against physical decline with an effect size of 0.62.[26] Exercise also slows decline in persons with Alzheimer's disease.[27] Aman and Thomas[28] found that supervised exercised reduced agitation in nursing homes.

Potential mechanisms by which exercise could improve cognitive function include changes in fitness, increased cerebral blood flow, reduction in depression, increase in presence or activity of neurotrophic factors [BDNF, insulin-like growth factor-1 (IGF-1)], downregulation of neurotoxic factors [C-reactive protein, cortisol, interleukin-6 (IL-6)] and other inflammatory cytokines and prevention or better control of chronic disease (e.g. stroke, diabetes, cardiovascular disease). Considering the non-robust nature of most of the interventions reported in Heyn *et al*.' s meta-analysis of cognitively impaired elders,[29] it does not appear that increases in aerobic capacity are required for cognitive benefits to accrue, as was previously thought. Cognitive benefits seen after non-aerobic exercise also cast doubt on a central role for aerobic capacity. The other mechanisms noted above appear more likely at this time. Exercise does increase cerebral blood flow acutely, as do cognitive tasks, and increased frontal cortex capillary density has been observed in animal models after exercise training, suggesting a possible common pathway for improved brain oxygenation and, thereby, function. Many of the most promising mechanisms in animal models have yet to be confirmed in human studies. Further exploration of the potential mechanisms of benefit in this crucial domain of health and function is needed, including studies linking changes in cerebral blood flow, depressive symptoms, physical fitness or burden of chronic disease and disability to cognitive changes associated with exercise participation.

Disease prevention through exercise

Both healthy and chronically ill older adults are candidates for preventive strategies that will lessen the burden of comorbidity, disability and premature death caused by incident disease. Physical activity patterns may be influenced by ageing and genotype and physical activity in turn may influence physiological capacity, psychological health, dietary intake, other adverse behaviours or risk factors for chronic disease. All of these are potential pathways by which exercise could ultimately influence the prevalence of chronic disease in a population. Other than genetic factors and environmental insults (pollution, asbestos, heavy metals, infectious agents, etc.), most of the major contributors to the development or severity of chronic diseases are in some way related to habitual levels of physical activity. Examples include cardiovascular disease, stroke, type 2 diabetes,[12] obesity, hypertension, osteoarthritis, depression[20] and osteoporosis. A notable exception to these patterns is the diseases of the central nervous system (CNS) (e.g. Parkinson's disease, other degenerative neurological diseases) that have not been substantively linked aetiologically with exercise or physical activity.

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

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

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

Randomized clinical trial data are available for the prevention of some disease states (cardiovascular disease, diabetes mellitus and falls) but are not yet available for others (stroke, osteoporotic fracture, depression). Diabetes is clearly preventable in high-risk obese adults with impaired glucose tolerance randomized to exercise and diet, as shown in the Finnish Diabetes Study[12] and the Diabetes Prevention Program (DPP).[30] Similarly to Finnish subjects, DPP participants randomly assigned to the intensive lifestyle intervention of diet and exercise reduced their risk of incident type 2 diabetes by 58% by 3 years. Of particular interest is the finding that those over the age of 60 years responded best, with a 71% reduction in incident diabetes in this time frame.

The major diseases and syndromes for which exercise may be beneficial as a preventive strategy are listed in Table 10.6, along with the postulated mechanisms of exercise benefit and the specific modality of exercise most relevant for these outcomes.

Evidence for the role of exercise in the treatment of disease

Mechanisms of benefit

There are many ways to conceptualize the integration of exercise into the treatment of established disease. For example, traditional medical interventions do not typically address disuse syndromes accompanying chronic disease, which may be responsible for much of their associated disability. Exercise is particularly good at targeting syndromes of disuse and may thus impact significantly on disability without altering the underlying disease itself in any primary way. Examples include Parkinson's disease, chronic obstructive pulmonary disease and chronic renal failure. Exercise may also lower the risk for recurrences of a disease, such as secondary events in patients with cardiovascular disease or prevention of recurrent injurious falls in an individual after a hip fracture. Some pathophysiological aberrations that are central to a disease are specifically addressed by exercise, which may therefore serve as an adjunct to standard care. For example, losses of visceral fat achieved through resistive or aerobic training improve insulin resistance and complement dietary and pharmacological management of type 2 diabetes in the older adult with central obesity.

Exercises designed to stimulate skeletal muscle hypertrophy in congestive heart failure provide benefit that counteracts the catabolic effects of circulating cytokines in this disease and is not achievable with cardiac medications alone. Functional improvements in individuals with arthritis who are given quadriceps exercises improve joint stability and may thus add to the benefits of anti-inflammatory and analgesic medications. It is not possible in this chapter to review every disease in which exercise has beneficial effects and therefore we will use type 2 diabetes as one example of the diseases outlined in Table 10.7.

Exercise in the treatment of type 2 diabetes

The prevalence of type 2 diabetes appears to be rising precipitously, linked to the rise in obesity throughout the world. Most of the individuals concerned have scope for lifestyle modification, in particular for suboptimal levels of physical activity. Cardiovascular disease accounts for half of the mortality in older type 2 diabetics,[31] emphasizing the complex clinical syndrome represented by this cohort.

The value of tight regulation of glucose in type 2 diabetics has been convincingly demonstrated in the UK Prospective Diabetes Study, among others.[32] This is particularly important in the elderly, who may have glucose intolerance and then diabetes for many decades and are therefore at extremely high risk for end organ damage due to glycosylation of body proteins. Although glycaemic control has been proven to be highly effective in controlling diabetes, the deleterious effects of central obesity and lack of exercise can undo the benefits of proper medical management and therefore may hasten the emergence of disease complications in susceptible individuals with insulin resistance. Weight loss diets are clearly central to the management plan of obese type 2 diabetics and may be aided by the use

Table 10.6 Potential mechanisms by which exercise can prevent disease.

Disease or syndrome	Postulated mechanisms of exercise effect	Recommended exercise modality
Arthritis	• Decreased body weight • Maintenance of cartilage integrity • Maintenance of muscle and tendon strength	Aerobic exercise[a] Resistance exercise[a]
Cancer (breast, colon, prostate)	• Decreased body fat • Decreased estrogen levels • Altered dietary intake • Decrease in gastrointestinal transit time • Increased prostaglandin F2	Aerobic exercise
Chronic renal failure	• Reduced risk of hypertension • Reduced risk of type 2 diabetes mellitus	Aerobic exercise Resistance exercise[a]
Congestive heart failure	• Decreased risk of ischaemic heart disease • Decreased risk of hypertension • Decreased risk of type 2 diabetes mellitus	Aerobic exercise[a] Resistance exercise[a]
Coronary artery disease	• Decreased blood pressure • Decreased LDL cholesterol • Increased HDL cholesterol • Decreased fibrinogen • Decreased total body fat, visceral fat • Decreased insulin resistance, hyperinsulinaemia • Decreased cortisol levels, inflammatory cytokines • Increased adherence to smoking cessation, dietary behaviours • Decreased depression, anxiety • Improved endothelial cell function	Aerobic exercise Resistance exercise
Dementia	• Improved cerebral blood flow • Increased neurotrophic factors in CNS • Hippocampal neurogenesis	Aerobic exercise
Depression	• Increased self-efficacy, mastery • Internalized locus of control • Decreased anxiety • Improved sleep • Increased self-esteem • Increased social engagement; decreased isolation • Decreased need for drugs associated with depression (beta-blockers, alpha-blockers, sedative hypnotics) • Decreased body fat, improved body image	Aerobic exercise Resistance exercise[a]
Osteoporotic fracture	• Increased bone density • Increased tensile strength • Increased muscle mass • Improved gait stability and balance • Improved nutritional intake (energy, protein, calcium, vitamin D) • Reduced fear of falling, improved self-efficacy • Increased overall activity levels, mobility • Decreased need for drugs associated with postural hypotension, falls, hip fractures (antidepressants, anti-hypertensives, sedative-hypnotics)	Resistance exercise[a] Aerobic exercise[a] Balance exercise[a]

(*continued overleaf*)

Table 10.6 (*continued*).

Disease or syndrome	Postulated mechanisms of exercise effect	Recommended exercise modality
Stroke	• Decreased obesity • Decreased blood pressure • Decreased cholesterol	Aerobic exercise Resistance exercise[a]
Type 2 diabetes mellitus	• Improved insulin sensitivity • Increased GLUT-4 protein and translocation to membrane sites • Reduced visceral fat mass • Decreased cortisol response to stress • Improved dyslipidaemia • Decreased blood pressure • Increased muscle mass	Aerobic exercise Resistance exercise (combined with diet and aerobic exercise)

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

of metformin as an appetite suppressant or acarbose as a means to decrease the extent of carbohydrate absorption. However, the difficulty of long-term weight management via dietary restriction is well known in the clinical setting, due to a variety of factors that impede such behavioural change in older adults. In addition, weight cycling due to repetitive attempts at sustained weight loss leads to losses of lean tissue (muscle and bone) and decreases in metabolic rate, thus worsening the energy balance equation in the end and making dietary management more and more difficult. Therefore, the standard care of obese type 2 diabetics leaves the majority of them suboptimally managed in relation to their primary metabolic derangement: *insensitivity to the action of insulin*.

All consensus panels recommend aerobic exercise as part of the management plan in type 2 diabetes. Moderate- or high-intensity aerobic exercise of 3–4 h per week results in improved insulin sensitivity and glucose homeostasis, assists in attainment or maintenance of lower body weight, reduces visceral fat depots, modestly improves blood pressure and lipids and lowers the risk of cardiovascular morbidity and mortality.

However, the clinical management of the obese elderly patient with this disease is often complicated by increasing insulin resistance and resultant polypharmacy, in addition to multiple other comorbid health conditions that impede compliance with both diet and aerobic exercise and reduce quality of life. For example, it would not be unusual for an older diabetic to present with obesity, osteoarthritis, ischaemic heart disease, hypertension, gout, hyperlipidaemia, peripheral vascular disease, sleep apnoea, peripheral neuropathy, a gait and balance disorder, functional impairment, renal disease, postural hypotension, bladder dysfunction, retinal disease and depression. Such *disease clustering* makes the application of standard dietary and exercise recommendations in addition to intense pharmacological management a challenge to practitioner and patient alike. It is not surprising that aerobic exercise recommendations, endorsed by all international consensus panels, are often difficult or impossible to implement in such patients. In particular, obesity, osteoarthritis, amputations, visual impairment, foot problems, fall risk, orthostatic hypotension, peripheral vascular disease and a low threshold for ischaemia may make aerobic exercise at the volumes and/or intensities shown to produce metabolic benefits in clinical trials unrealistic in practice.

An alternative approach to aerobic exercise recommendations for diabetics is the use of progressive resistance training. Insulin resistance is worsened by loss of muscle mass, decreased glucose transport into skeletal muscle and subsequent glycogen storage, catabolic/inflammatory mediators, inactivity, visceral fat and related inflammatory cytokines such as IL-6 and C-reactive protein. The specific indications for resistance training in older diabetics include its ability to combat age and diabetes-related sarcopenia, to prevent loss of muscle and bone mass and reduced resting metabolic rate which otherwise accompanies hypocaloric dieting, to increase glucose uptake and storage in skeletal muscle, to reduce visceral fat depots, to reduce C-reactive protein, as well as its beneficial effects on resting blood pressure, functional status, mobility, sleep and depressive symptoms. The effects on muscle mass are unique to high-intensity resistance training and clearly distinguish it from aerobic exercise. For this reason, some experts are currently recommending its addition to recommendations for aerobic exercise and dietary modification. A review of the randomized controlled trial evidence upon which such recommendations are made is presented in

Table 10.7 Exercise and disease treatment.

Disease state	Exercise of choice	Considerations
Arthritis	Aerobic	Low impact
	Resistance training	Sufficient volume to achieve healthy weight if obese
Chronic insomnia	Aerobic	Exercise 4–6 h before desired bedtime to maximize effects
	Resistance training	
Chronic obstructive pulmonary disease	Aerobic	Resistance training may be more tolerable in severe disease; combined effects complementary if feasible
	Resistance training	Time exercise sessions to coincide with bronchodilator medication peak
		Use oxygen during exercise as needed
Chronic renal failure	Aerobic	Exercise reduces cardiovascular and metabolic risk factors, improves depression
	Resistance training	Resistance training offsets myopathy of chronic renal failure
Congestive heart failure	Aerobic	Resistance training may be more tolerable if dyspnoea severely limits aerobic activity
	Resistance training	Cardiac cachexia targeted by resistance training
Coronary artery disease	Aerobic	Complementary effects on exercise capacity and metabolic profile from combined exercise modalities
	Resistance training	Resistance training may be more tolerable if ischaemic threshold is very low due to lower heart rate response to training
Depression	Aerobic	Moderate- to high-intensity exercise more efficacious than low-intensity exercise in major depression
	Resistance training	Minor depression may respond to wider variety of exercise modalities and intensities
Hypertension	Aerobic	Small–moderate reduction in systolic and diastolic pressures seen
	Resistance training	Larger changes if weight loss occurs
Obesity	Aerobic	Sufficient energy expenditure to induce deficit
	Resistance training	Resistance training maintains lean tissue (muscle and bone) better than aerobic training during weight loss
Osteoporosis	Aerobic	Aerobic exercise should be weight bearing
	Resistance training	High-impact, high-velocity activity (e.g. jumping) potent if tolerable; avoid if osteoarthritis present
	Balance training	Resistance training effects are local to muscles contracted
		Balance training should be added to prevent falls
Peripheral vascular disease	Aerobic	Vascular effect is systemic, upper limb ergometry may be substituted for leg exercise if necessary
		Resistance training has positive but less robust effect on claudication
		Need to exercise to the limits of pain tolerance each session to extend time to claudication
Venous stasis disease	Aerobic	Local muscle contractions stimulate return of fluid via lymphatic system
	Resistance training	Utilize lower body training, elevate legs when possible

Table 10.8. Although there is strong preliminary evidence that weight-lifting exercise improves metabolic control and cardiovascular risk factors in type 2 diabetes, to date there have been only two published randomized controlled trials of resistance training as an *isolated* intervention to augment usual care in type 2 diabetes.

Exercise to counteract iatrogenic disease

Finally, exercise may counteract undesirable side effects of standard medical care, a use of exercise that is just emerging in the literature. Such use of exercise would include resistance training for patients receiving corticosteroid treatment to counteract the associated proximal myopathy and osteopenia, neutralizing the adverse effects of energy-restricted diets in obesity or protein-restricted diets in chronic renal failure,[41] for example.

Osteopenia associated with corticosteroid usage appears to be completely eliminated by concurrent progressive resistance training, which should be recommended for all such patients. Although bisphosphonates have also been shown to be very effective for corticosteroid osteopenia, they do not address the coexisting steroid myopathy, as resistance training does, and are therefore an insufficient antidote for corticosteroid side effects. An excellent target group for such health promotion efforts would be older

Table 10.8 Randomized controlled trials including resistance training in type 2 diabetes.

Study	*N* (average age)	Duration of training (months)	Resistance training intensity	Other additional intervention	Significant improvement in insulin sensitivity or glucose homeostasis
Dunstan *et al.*[33,34]	36 (60–80 years)	2 (6 months supervised)	High	Moderate weight loss programme	Yes, for supervised phase but not home-based, free-weight phase
Balducci *et al.*[35]	120 (60.9 years)	12	Moderate	Aerobic at 40–80% HR	Yes
Baldi and Snowling[36]	18 (46.5 years)	2.5	Moderate	None	Yes
Cuff *et al.*[37]	28 (60.0 years)	4	Low	Aerobic at 60–75% HR	Yes
Loimaala *et al.*[38]	50 (53.3 years)	11	High	Aerobic at 65–75% HR	Yes
Attema *et al.*[39]	85 (age not reported)	6	High	Aerobic at 75% HR	Yes
Castaneda *et al.*[10]	62 (66 years)	4	High	None	Yes
Dunstan *et al.*[40]	27 (51 years)	2	Moderate	Low-intensity cycling between each set	Yes

men with steroid-dependent chronic lung disease, in whom pulmonary cachexia, malnutrition, tobacco use, steroid myopathy and osteoporosis combine to produce profound wasting, osteoporotic fracture and impaired exercise tolerance. Aerobic training will improve functional status in this clinical cohort, but is insufficient to address the musculoskeletal wasting.

Exercise and the prevention and treatment of disability

There are many ways in which physical activity may influence the development and expression of disability in old age. These theoretical relationships are now borne out in many epidemiological investigations and provide the rationale for both the experimental studies and exercise recommendations that are found in many recent reviews of this topic. For example, 1097 participants from the Established Populations for Epidemiological Studies of the Elderly (EPESE) study who were not disabled at baseline were analyzed for factors related to disability-free survival until death in old age. Physically active adults were more likely to survive to age 80 years or beyond and had approximately half the risk of dying with disability compared with their sedentary peers.

The most obvious conclusion from a review of the literature in this area is that there is a great deal of overlap between the identifiable risk factors for disability and the consequences or correlates of habitual inactivity. At the most basic level, shared demographic characteristics between those at risk of disability and those more likely to exhibit sedentary behaviour include advanced age, female gender, non-Caucasian ethnicity and lower educational level and income. Psychosocial features common to both cohorts include social isolation, low self-esteem, low self-efficacy, depressive symptoms and anxiety. Lifestyle choices more prevalent in disabled and/or inactive adults include smoking and excess alcohol consumption. Body composition changes associated with both functional decline and inactivity include sarcopenia, obesity, visceral obesity and osteopenia. Exercise capacity is typically reduced in both conditions in all domains, including aerobic capacity, muscle strength, endurance and power, flexibility and balance. Gait instability and slowness, and also impaired lower extremity function and mobility, characterize both disabled and inactive populations. Since most studies have not assessed the full complement of factors known to be associated with disability and many have made observations at a single point in time, it is not possible to say with certainty how all of these complex relationships fit together, which relationships are causal and which risk factors are independent of each other.

In addition to the associations above, chronic diseases associated with inactivity, such as obesity, osteoarthritis, cardiovascular disease, stroke, osteoporosis, type 2 diabetes, hypertension and depression, are all risk factors for disability as well. In some cases, data linking inactivity to disability-related diseases are available from cross-sectional or prospective cohort studies and also experimental trials [e.g. diabetes, cardiovascular disease and in other cases from epidemiological data alone (colon and breast cancer[42])]. Disability is complex and not fully explained by deficits in physical capacity such as strength and balance and other pathways may be operative, including sensory function, glycaemic control, psychological constructs and other aspects of health status.

Recent prospective and experimental studies have strengthened the hypothesized causal relationship between sedentariness, functional limitations and disability in older adults. Miller *et al*. reported results from 5151 participants in the Longitudinal Study of Aging[43] and showed that physical activity results in a slower

progression of functional limitations and thereby slower progression to ADL/IADL disability at 6 months of follow-up after the intervention ended. In the largest reported randomized controlled trial of exercise and disability to date,[44] 704 residents of nine different nursing homes were randomized into resistive exercise, nursing rehabilitation or control conditions. After 17 months, residents in both intervention homes had significantly less decline in ADL functioning than those in control homes.

Tai chi improves balance, reduces falling and fear of falling and increases walking speed.[45]

A review of studies targeting disability in disease-specific populations such as depression, cardiovascular disease, stroke, chronic lung disease and arthritis is beyond the scope of this review, but there is evidence that exercise is beneficial in all of these conditions as a primary or ancillary treatment. The largest body of data exists for older adults with osteoarthritis, which is the commonest condition related to disability in the elderly. Five of the 11 randomized controlled trials reported up to 1999 demonstrated improvements in disability scores relative to controls in trials from 4 weeks to 18 months in duration. Weight-bearing functional exercises, walking and resistance training were used in various combinations in these studies and there is no clear indication of the superiority of one modality over another in the reduction of pain and disability from osteoarthritis. It is likely that the disability reductions in arthritis are due to the impact of exercise on a variety of factors, including muscle strength, gait and balance, body weight, pain, comorbid disease expression, self-efficacy and depressive symptoms, among others.

Conclusion and directions for future research

There are sufficient data from both epidemiological studies and experimental trials to warrant the training of all physicians, including geriatricians, in the basics of exercise prescription for health-related and quality of life benefits, as outlined in Table 10.9.

Screening for sedentariness should take place at all major encounters with healthcare professionals, given its role as a potent risk factor for all-cause and cardiovascular mortality, obesity, hypertension, insulin resistance, cardiovascular disease, diabetes, stroke, colon cancer, depression, osteoporosis, recurrent falls and disability, among other conditions. Exercise recommendations should be integrated into the mainstream of other healthcare recommendations, rather than being marginalized as at present. Exercise advice should be specific in terms of modality, frequency, duration and intensity, accompanied by practical implementation solutions and behavioural support systems for monitoring progress and providing feedback. Ultimately, the penetration of these recommendations into the most inactive cohorts in the community, who have the most to gain from increases in levels of physical activity and fitness, will depend on a combination of evidence-based guidelines coupled with health professional training and

Table 10.9 Exercise recommendations for optimal ageing and prevention and treatment of disease in older adults.

Modality	Resistance training	Cardiovascular endurance training	Flexibility training	Balance training
Dose				
Frequency (days per week)	2–3	3–7	1–7	1–7
Volume	1–3 sets of 8–12 repetitions, 8–10 major muscle groups	20–60 min per session	Major muscle groups 1 sustained stretch (20 s) of each	1–2 sets of 4–10 different exercises emphasizing dynamic postures[a]
Intensity	15–17 on Borg Scale (70–80% 1RM), 10 s per repetition, 1 min rest between sets	12–13 on Borg Scale (40–60% heart rate reserve or maximum exercise capacity)	Proprioceptive neuromuscular facilitation (PNF) technique[b]	Progressive difficulty as tolerated[c]

[a]Examples of balance-enhancing activities include tai chi movements, standing yoga or ballet movements, tandem walking, standing on one leg, stepping over objects, climbing up and down steps slowly, turning, standing on heels and toes, walking on compliant surface such as foam mattresses, maintaining balance on moving vehicle such as bus or train and so on.

[b]PNF involves stretching as far as possible, then relaxing the involved muscles, then attempting to stretch further and finally holding the maximum stretch position for at least 20 s.

[c]Intensity is increased by decreasing the base of support (e.g. progressing from standing on two feet while holding on to the back of a chair to standing on one foot with no hand support); by decreasing other sensory input (e.g. closing eyes or standing on a foam pillow); or by perturbing the centre of mass (e.g. holding a heavy object out to one side while maintaining balance, standing on one leg while lifting the other leg out behind the body or leaning forwards as far as possible without falling or moving feet).

behavioural programmes tailored to age-specific barriers and motivational factors.

Key points

- The reduction in exercise capacity typical of the older adult is largely explained by reduced muscle mass and function, decreased maximum heart rate and cardiac output and impairment of central and peripheral nervous system processing, recruitment and conduction velocity.
- Ageing and a sedentary lifestyle or disuse syndromes have very similar effects on a multitude of physiological changes attributed to chronological age which reduce exercise capacity.
- Habitual physical activity increases average life expectancy by ~2 years, but the mechanism of this effect is probably multifactorial and not precisely defined.
- Prevention of many of the typical changes attributed to biological ageing is possible with chronic participation in physical activity, particularly alterations in body composition: decreased muscle mass, decreased bone mass and strength, increased adipose tissue mass and its central deposition.
- Prevention and/or treatment of many of the most common chronic diseases which afflict older adults, including obesity, cardiovascular disease, type 2 diabetes, hypertension, osteoarthritis, osteoporosis, stroke, peripheral vascular disease and depression are possible with targeted, robust doses and modalities of exercise.

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CHAPTER 11

Health literacy and cultural sensitivity

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Introduction

Dramatic shifts in population demographics due to migration have led to the requirement that health professionals acquire cultural sensitivity in addition to medical acumen in geriatric health care. A dramatic example of the effects of migration can be seen in the United Kingdom (UK). In the 1950s, Bethnal Green, an area in London, was a predominantly white, working-class neighbourhood, whereas in the 1990s it had changed to Tower Hamlets, the home of large numbers of Bangladeshi immigrants. Wolverhampton, in the West Midlands, UK, has a significant multicultural nature. It has an above-average level of non-Christian religions (13.6% of people, compared with 5.5% for England and Wales). Sikhs account for 7.6% of Wolverhampton's population. The number of Hindus is also higher than the England and Wales average (Wolverhampton 3.9%, England and Wales 1.1%). Leicester is one of the oldest cities in the UK and is also one of the most ethnically diverse. It has small communities of Poles, Irish, Indians from the Indian sub-continent, Kenya and Uganda, Dutch citizens of Somali origin and a significant number of East European migrants. The Commission for Racial Equality (CRE) estimated that by 2011 Leicester will have approximately a 50% ethnic minority population, making it the first city in Britain not to have a white British majority. Changes such as these require training programmes for health professionals in how beliefs of different cultures may impact the interactions between older persons and their health care providers.

The ultimate goal of geriatric care providers is to provide good medical care to all older patients. This goal is made difficult when patients do not possess adequate health literacy, that is, the ability to understand and manage their own health care. Good communication is so critical to improving health literacy. When the cultural characteristics of both patients and providers are so different that communication is compromised, poor health literacy is likely to make it difficult for patients to receive good health care. This chapter presents ideas on how cultural context affects the provision of health care to an ageing, multiethnic population. Collaboration between providers and the patients and their caregivers becomes even more important in these circumstances. This chapter addresses some of the barriers to accomplishing the goal of providing good health care that arise from cultural differences. Suggestions on how to minimize cultural differences in the clinical encounter will be given. Because there is so much cultural diversity worldwide, this chapter will serve as a reminder that the problem must be addressed, rather than provide a laundry list of solutions. A list of resources at the end of the chapter will help guide practitioners in the development of their own strategies to develop and maintain cultural sensitivity with the goal of improving health care to their multicultural patient base.

The importance of health literacy in health care

Health literacy is a relatively recent concept to be discussed in the health care literature. It refers to individuals' ability to understand and manage their personal health care issues. This is of great concern because individuals with limited health literacy have less health knowledge, worse self-management skills, lower use of preventive services, especially for those aged 65 years and older,[1] and higher hospitalization rates. Much research has confirmed that many individuals in the geriatric patient population are at risk of inadequate or marginal health literacy.[2] In the United States, one in three persons has low health literacy.[3] In Australia, depending upon the health literacy assessment tool used, between 7 and 25% of the general population had less than adequate health literacy.[4]

Factors that influence health literacy

Multiple factors influence health literacy (Table 11.1). Factors such as increasing age, less education, lower income, 'blue collar' jobs and poor health status (both mental

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 11.1 Common factors affecting health literacy.

- Age
- Education
- Cognitive Status
- Gender
- Income
- Race
- Health Status
- Vision
- Hearing

and physical) can all put people at risk for marginal or inadequate health literacy.[5] This risk impacts health outcomes and therefore the cost for caring for older persons. Limited health literacy is associated with low socioeconomic status, comorbidities and poor access to health care, suggesting that it may be an independent risk factor for health disparities in older people.[6] Lower literacy was more common among African Americans, older patients and patients who required medication assistance.[7] Poor health literacy has dire consequences (Table 11.2). Among community-dwelling older adults who had recently enrolled in Medicare, inadequate health literacy was independently associated with poorer physical and mental health.[8] Older patients are particularly affected by health literacy issues because their reading and comprehension abilities are influenced by their cognition and their vision and hearing status. Inadequate health literacy can result in difficulty in accessing health care, following instructions from a physician and taking medication properly. Patients with inadequate health literacy are more likely to be hospitalized than patients with adequate skills.[9]

Functional literacy declines with age.[10] Home interviews conducted with community-dwelling elderly persons (n = 2774) found that a significant decrease in health literacy was associated with every year increase in age, even following adjustments for gender, race, ethnicity, cognitive status and education. Differences in newspaper reading frequency, visual acuity, chronic medical conditions and health status did not explain the lower literacy of older participants. Both health literacy and cognitive abilities independently predict mortality. Interventions to improve patient knowledge and self-management skills should consider both the reading level and cognitive demands of the materials.[11] Memory and verbal fluency are strongly associated with health literacy, independently of education and health status, even in those with subtle cognitive dysfunction. Reducing the cognitive burden of health information might mitigate the detrimental effects of limited health literacy in older adults.[12] In addition, there are age differences in knowledge, as shown by Farrer *et al*.[13] in a study on mental health literacy. In Australia, this study showed that a community's knowledge and beliefs about mental health problems, their risk factors, treatments and sources of help varied as a function of age. Older adults (70+ years) were poorer than younger age groups at correctly recognizing depression and schizophrenia. Older respondents were more likely to believe that schizophrenia could be caused by character weakness.[13]

Table 11.2 Consequences of low health literacy.

- Poorer physical health
- Poorer mental health
- Difficulty accessing health care
- Difficulty following instructions from a physician
- Difficulty taking medications properly
- Increased hospitalisations
- Premature mortality

The role of education in health literacy

Education plays a key role to overcoming the effects of poor health literacy. If health information is shared via spoken instruction, it is best to remember that older patients understand medical information better when spoken to slowly, simple words are used and a restricted amount of information is presented. Often health literacy is addressed using written materials. However, in the United States, many older adults read at an eighth-grade level and 20% of the population reads at or below a fifth-grade level. A study of 177 low-income, community-dwelling, older adults (with no cognitive or visual impairments) was carried out to determine whether they had difficulty in understanding written information provided by clinicians. The subjects' mean reading skills were at fifth-grade level, below those of the general American population. One-quarter of subjects reported difficulty in understanding written information from clinicians.[14] However, most health care materials are written at a tenth-grade level.[5] Health care providers must identify patients with marginal or inadequate health literacy and adjust their health care education strategies to meet these literacy needs. For optimal comprehension and compliance, patient education material should be written at a sixth-grade or lower reading level, preferably including pictures and illustrations.[9] It is also important to provide instruction in the language in which the patient is most fluent. For example, compared with those with adequate and marginal health literacy, women with inadequate functional health literacy in Spanish were significantly less likely to have ever had a Papanicolaou (Pap) test.[15] Of course, having assessment tools translated into the original language does not solve problems with health literacy. In Turkey, in a clinic where 2.7% of patients had inadequate (less than or equal to sixth grade) health literacy, 38.6% had marginal (seventh to eighth grade) and 58.7%

(greater than or equal to ninth grade) had adequate health literacy. Being female, primary school educated, in poor economic condition and older were all risk factors for the lowest level of health literacy.[16] Cordasco *et al*.[17] recruited 399 English- and Spanish-speaking inpatients being evaluated or treated for congestive heart failure or coronary artery disease at a large, urban safety-net teaching hospital in Southern California. They compared by age (aged 65 years or more, 51–64 years and less than 50 years), levels of health literacy, educational attainment, English comprehension and language use and found that the prevalence of inadequate health literacy increased significantly with increasing age. The correlation between older age and lower health literacy persisted when controlling for educational achievement, race, ethnicity, gender and immigration status. Additionally, older patients were more likely to have never learned to read, to have no formal education, to have limited English comprehension and to speak a non-English language at home. This study suggests that in order to meet the chronic disease needs of a growing older, multiethnic patient population and ameliorate the negative health effects of associated low literacy, safety-net hospital leaders and providers need to prioritize the development and implementation of low-literacy educational materials, programmes and services.[17] Finally, differences in mental health literacy across the adult lifespan suggest that more specific, age-appropriate messages about mental health are required for younger and older age groups.[13]

Educational strategies to improve health literacy

Fortunately, proper educational techniques (Table 11.3) can make a difference in health care for persons with low health literacy.[7] Of 111 patients with poorly controlled diabetes, 55% had literacy levels at the sixth grade level or below. Over the 6 month study period, patients with low and high literacy had similar improvements in A1C when they received one-to-one education and medication management for these patients using techniques that did not require high literacy from clinic-based pharmacists. Among community-dwelling Korean older adults, limited health literacy was associated independently with higher rates of chronic medical conditions and lower subjective health status. Nurses were found to be key to providing health education to these older adults[18] to help them maintain their independence. The greatest potential barrier to addressing health literacy is the fact that most patients are often unwilling to admit that they have literacy problems.[9] Indeed, Weiss et al found that 97% of their research subjects, regardless of literacy level, reported that television was their primary source of information.[14]

Table 11.3 Educational techniques to improve health literacy.

- Written material
  - At sixth grade level
  - In primary language of patient
  - Uses simple words
  - Is age appropriate
  - Includes pictures and illustrations
  - Presents a small amount of information
- Auditory material
  - Delivered slowly
  - Is delivered one-on-one
  - Is in the patient's primary language
  - Is delivered by a trusted provider

Cultural sensitivity in geriatrics

The need for cultural sensitivity

Developing strategies to increase awareness of cultural differences and to address them appropriately in the context of providing good health care is difficult because of the various influences on culture (Table 11.4). This goal is further complicated by the fact that culture is fluid and constantly changing. These changes compound misunderstandings between members of different cultural groups. A further complication is the fact that there are cultural differences between the different generations of people who share the same cultural background. Also, cultural differences often seem to be insurmountable between men and women of the same cultural background. Gender differences across cultures can be even more complicated. These differences highlight the complicated and constantly changing nature of culture. Geriatrics requires that the health care providers interact with multiple generations of the same family. Therefore, any general strategies employed to address cultural differences in the clinical setting need to be general and flexible in approach.

When cultures clash

Culture surrounds and defines everyone. Both providers and patients have their own national and ethnic cultures. These cultures include their culture of origin and also those

Table 11.4 Cultural factors that affect health care.

- Age
- Gender
- Ethnicity
- Assimilation
- Generation cohort
- The ever changing nature of culture

cultural values, beliefs, language and skills of the local culture (acculturation) that they have adopted. The patients' cultures will influence when they seek treatment, what their expectation of care will be and whether or not they will comply with the providers' recommendations.[19] Health care providers have the culture of biomedicine in general and that of their specific profession (e.g. medicine, nursing and pharmacy) and specialty (e.g. surgery, geriatrics and rheumatology) in particular. In addition, both providers and patients have cultural ideas and values that relate to their social culture,[20–22] age,[23,24] gender[25,26] and gender identity.[27,28] Finally, health care providers for geriatric patients are almost always younger than their patients. This age difference also has ramifications in compliance based on trust and respect.[29]

Finding a way to communicate effectively is critical to good patient care. Patient satisfaction and the likelihood of compliance with medical instructions[30,31] are linked to patient–provider communication. If cultural differences are not addressed, then poor health outcomes and limited quality of medical decision-making may result.[32] Patient satisfaction with health care is affected by age, race and literacy level. In low-income populations, communication satisfaction may be lower for groups that are traditionally active in doctor–patient interactions (e.g. younger patients, patients with higher literacy skills). Health care providers should be aware that older, non-white, optimistic and literacy deficient patients report greater communication satisfaction than their younger, white, pessimistic and functionally literate peers and are more likely to cope with their illnesses by withdrawing rather than by actively pushing for a higher standard of care.[33] Therefore, health care providers should continuously seek ways to facilitate dialogue with patients who are older, non-white and have poor literacy skills. Thus, cultural sensitivity can help providers improve health care delivery in the clinical encounter. It can lead to better provider–patient communication, more accurate diagnosis, more effective treatment, higher patient satisfaction/compliance and efficient use of medical resources.

For most adults who are not health care providers themselves, navigating the culture of biomedicine is challenging. These challenges are exacerbated for older adults who are handicapped with physical, mental and/or social limitations. Most older adults suffer with chronic diseases in addition to acute diseases. The physical burdens that these chronic diseases put on older persons, especially if they have low health literacy, are often underappreciated by health care providers. For example, community-dwelling Korean older adults with low health literacy often have been reported to have significantly higher rates of arthritis and hypertension. After adjusting for age, education and income, older individuals with low health literacy had higher limitations in activity and lower subjective health. Older individuals with low health literacy were more likely to report lower levels of physical function and subjective health and higher levels of limitations in activity and pain.[18] Nor are the patients themselves the only ones with challenges. The providers have their own challenges when applying their biomedical culture to an ageing population. They were taught '*Primum non nocere*' (or 'First, do no harm', the origins of which are discussed elsewhere[34]), but many cures are harsh. This is because so many cures are designed for younger, robust patients who are experiencing an acute illness, and who have natural reserves that will allow them to overcome any debilitating effects of the 'cure'. This is not true for the frail elderly. For them, multiple pharmaceuticals increase the possibility of lethal drug interactions and/or side effects. Surgery is dangerous and the subsequent recovery can be debilitating. Medical care is expensive and cannot be paid for by everyone. Sometimes the care is available but not always in a timely manner. This waiting period can be particularly problematic for an older person, especially is he/she lacks the cultural understanding of the need for haste or confrontation. Finally, the culture of medicine often emphasizes the quantity of life over the quality of life. However, older patients may insist upon more autonomy than the culture of biomedicine encourages.[35] They do not always follow instructions, especially if they feel that quality of life is preferred over quantity of life. It is not uncommon for family members to decide that an older patient should not be treated of a serious disease such as depression[26] or cancer.[36,37] This makes treatment difficult, if not impossible.

These differences in the approach to the culture of medicine affect care. Being aware of the potential for culture-related problems in the clinical encounter is the first step in developing strategies to deal with those problems when they arise. To address these differences, providers must learn to communicate effectively, to provide evidence-based medicine in a timely manner, to be prepared continually to develop new health services that target older adults' changing medical needs and to consult with the older patient and family as to their preferences for care. The delivery of optimal health care depends upon understanding across all cultures.

Barriers to cultural understanding

There are several barriers to developing successful strategies for the delivery of health care (Table 11.5). First, it is impossible to learn about every cultural or ethnic group that might seek health care. Second, relying on cultural stereotypes for guidance can result in conflict with those patients who show within-culture variations or who have acculturated to the local norms. Third, if culture is viewed as an obstacle to be overcome, rather than incorporated into the care plan, then conflicts cannot be resolved. Finally, if the impact of the culture of biomedicine on provider–patient

Table 11.5 Barriers to successful culturally appropriate health care delivery.

- Large variety of cultures
- Effects of acculturation
- Negative effects of stereotypes
- Complexity of the culture of biomedicine

communication[38] is ignored, then problems with health literacy arise. Any of these barriers may lead to a failure either in compliance or in the application of the best medical solution.

Hence cultural sensitivity is more a process than an outcome. It is as much about acceptance of differences as it is about knowledge of differences. The following section lists a number of common problems that may arise in clinical encounters between people with different cultural experiences. The subsequent section provides general strategies for addressing these problem areas.

Common areas of conflict or misunderstanding in the clinical encounter

There are several areas in which misunderstandings commonly occur during a clinical visit (Table 11.6). Each of these is described below along with suggestions for improvement.

Prior experiences

Both the provider and the patient bring certain expectations to the clinical encounter based on prior experience. Both may be unaware that their own ethnic or professional culture has an influence on the interaction. Problems often arise due to the knowledge and power differential between the patient and the provider.

Patients may distrust their providers based on their own or significant others' previous encounters with biomedicine, such as the American experience with the Tuskegee Syphilis Study. This unfortunate research study exemplifies several factors that have influenced African American's attitudes toward the biomedical community in the United States,[39] although more recent research indicates that these attitudes may have ameliorated over the past two decades.[40] This may be due to acculturation by the younger generation, rather than forgiveness on the part of those who were directly affected.

Table 11.6 Common areas of cultural conflict.

- Mistrust garnered during prior contacts
- Cultural differences in defining who the patient is
- Verbal and non-verbal communication
- Prior misconceptions about cultural norms
- Ageism by both patient and provider

Providers may view the patients' ethnic cultures as an obstacle. For example, because Afghani Muslim women do not seek health care from male practitioners,[26] the woman receives care by proxy. Her husband describes her symptoms to the male practitioner, who then instructs the husband in the recommended treatment plan. Not all practitioners are comfortable in practicing medicine in this manner.

Identifying the patient

In general, Western biomedical culture focuses on the adult individual as the patient. As such, information is gathered from the patient and the patient alone (this is different from practicing Western paediatrics, where the mother and child are often considered to be the 'patient'). In many cultures, however, the family, or even the entire community, plays a major part in managing illness. In cases such as this, it is often best to include the entire family in decision-making,[41] including spouses and/or adult children.

Communication

Communication may be verbal or non-verbal and both are important. When communication is hindered by a lack of a common language, health suffers. Patients not proficient in the local language are unable to take advantage of health promotion programmes.[42,43] The clinician's misunderstanding of the patient's language can lead to inappropriate treatment,[44] ranging from misdiagnosis to ineffective pain control.[23]

Although professional translators may be employed, providers must remember that misinterpretations may occur even when the same language is spoken. Providers tend to mix medical jargon and everyday language when they speak to patients, but a word may mean something different than intended to the patient. For example, a patient may refer to a stomach ache, which is duly interpreted to be a pain in the stomach. The patient may actually mean a pain in the abdominal area. The clinician should be careful when interpreting the symptoms as they are reported. This is particularly true when the interpreter is a child who may not have insight into how important it is to have an accurate description of the symptoms, even if the patient is uncomfortable sharing that information with either the clinician or the child.

A surprising amount of information can be communicated through non-verbal cues. This has led to the successful development of pain assessment tools for demented patients.[45] Research on such tools provides information about which non-verbal assessment tools are most representative of the current state of the science, are most clinically relevant and are practically applicable to integrate into everyday practice and support adherence to regulatory

guidelines. Communication in the clinic is less well studied but certain areas of potential differences should be noted. For example, patients with different cultural backgrounds may have different ways of expressing distress. Some value stoicism whereas others value the open expression of pain. The presence of non-verbal behaviours such as reductions in activity, social withdrawal, self-protective manoeuvres, increased alterations in facial expressions or body postures and observable displays of distress in a stoic patient, who reports no such problems, would assist a provider in diagnosing unreported problems. The lack of these non-verbal behaviours in a patient reporting that their symptoms are severe might identify a patient from a more expressive culture.[46]

Other potentially problematic areas of non-verbal communication between persons with different cultural backgrounds include the pace of conversation, whether interruptions are encouraged, the degree of physical proximity of the provider to the patient during history taking and whether eye contact is appropriate or disrespectful. An interesting unintended consequence of the introduction of the electronic record is the perception on the part of some patients that it is disrespectful of the clinician to interact with the computer screen more than with the patient.[47] It is important to remember that the etiquette of touch, hand gestures and finger pointing varies across cultures. Another area with wide cultural variability is attitudes toward the direct discussion of death and dying, among both clinicians and patients and their families.[48]

Stereotyping

Sometimes a little knowledge is a dangerous thing and can lead to stereotyping.

Instead of trying to memorize what is appropriate for every culture, a brief conversation with the patient or interpreter can clarify what is acceptable and what is not and can clarify major points of potential conflict. Such a conversation would ideally take place during the initial visit of the patient. A special place in the patient record could be the repository of such information, along with a reminder to refer to that note before the patient is seen. Because culture is fluid and changes with social interactions, brief follow-up conversations about potential changes or to confirm previous conclusions would be appropriate at each office visit. It is important to understand that there is variation within cultural groups. There is no substitute for asking the patient what his/her treatment goals are.

Age

Very few health care providers are as old as their older patients. Therefore, there is limited personal experience with or insight into the nature of ageing and the consequences of chronic disease that the provider brings to the provider–patient relationship. Thus, the nature of ageing may be stereotyped by young health care providers. They may exaggerate the meaning/impact of functional differences, the consequences of chronic illnesses and the degree to which disabilities that increase with age affect the patient's quality of life. As a result, there is a risk that providers might fail to recommend lifestyle changes involving smoking cessation, good nutrition and exercise that might help patients to continue to live independently for many more years. Alternatively, older patients may disregard the expert advice of health professionals who are significantly younger than they are (reverse stereotyping) because they feel that the provider does not understand ageing due to a lack of personal experience.

Increasing cultural sensitivity in the clinical encounter

Increase self-awareness

Everyone has a culture. It is important to remember that the provider brings an ethnic and/or national culture to a clinical encounter, in addition to the biomedical culture. Approaching the patient as a cultural equal will reduce conflict between cultures. A sense of humour about small misunderstandings is crucial. Asking for explanations about the patient's culture and offering explanations to the patient about the biomedical culture shows good will and a desire to communicate. None of the cultures involved are problems to be overcome. Rather, they are opportunities for sharing.

Be prepared to address potential cultural differences when they arise. Not all patients identify strongly with their ethnic culture. Educational level, dominant language, religion, gender, year of immigration and even personality may have more of an effect on interactions with health care providers than cultural identity.[49] The best way to find out what influences the patients' cultures have on their health is to ask them directly and listen carefully to what they have to say.

Improve communication

The simple mnemonic ETHNIC(S) (Table 11.7) provides an easily remembered framework for providers to use in providing culturally appropriate geriatric care.[50] ETHNIC(S) can serve as a clinically applicable tool for eliciting and negotiating cultural issues during health care encounters. Geriatrics health care providers need to be aware of the effect that culture has on establishing treatment priorities, influencing adherence and addressing end-of-life care issues for older patients and their caregivers.

Explanation

It is the job of the practitioner to elicit explanations from the patient as to why he/she is seeking care. This may be achieved by asking direct questions about what they think

Table 11.7 ETHNIC(S) mnemonic for improving communication.

Explanation
Treatment
Healers
Negotiate
Intervention
Collaborate
Spirituality/seniors

the symptoms indicate and/or by asking direct questions about what they think family members or other sources may have suggested. It is a rare patient who is unaffected by the television or the Internet. This is a good time to evaluate how well the patient understands the symptoms and what he/she is worried about.

Treatment
Ask what the patient has already tried to alleviate symptoms and specifically mention some commonly used complementary and alternative medicine treatments. All patients have home remedies that are used when a symptom first presents. Sometimes those remedies are helpful and sometimes they are harmful.

Healers
This is an opportunity for providers to indicate to the patient that they understand that they may not be the sole health care provider for the patient. Knowing who the other healers are goes a long way towards knowing who needs to be included in the treatment plan when applying more complicated remedies.

Negotiate
Recovery from an illness requires teamwork, especially with the older patient. Informal caregivers may need to be engaged in the healing process. The provider needs to know how much of a partner the patient intends to be in his/her recovery.

Intervention
The degree to which the patient is willing to participate in the proposed medical interventions must be determined. If compromises must be made based on cultural conditions or if misunderstandings can be resolved, then the planned interventions can be implemented or modified in a timely manner.

Collaborate
Not only do the patient and provider need to work together, but informal caregivers and family members, other healers, other members of the interdisciplinary geriatric health team and community services must also all be included. Continuum of care for older persons is very much a team endeavour. Effective collaboration from the beginning makes the transitions easier.

Spirituality/seniors
Spirituality is an often unappreciated aspect of health care in older persons for both providers and patients. The provider should take the lead in asking whether the patient would like to discuss the role of his/her beliefs in his/her health care. This is particularly important in the case of end-of-life care.

Understand non-verbal cues
Communication goes beyond language and medical jargon. The use of technical terms should be minimized in order to ensure patient understanding. Care must be taken to understand when common terms such as 'stomach' may be used to refer to a different part of the abdominal area. The observation of non-verbal cues such as pointing or guarding of a body area will assist in locating areas of concern even when a common word cannot be found to describe the location of an illness or pain.

Use professional translators when possible
It is usually advisable to engage a professional translator or to use translated written materials for patients who are not fluent in the language commonly spoken in the medical office. Although it may be tempting to ask for help from a young relative who accompanies the patient, this is seldom advisable. Children as translators are especially problematic, especially if the medical topic may be construed as not appropriate for a child. That said, sometimes even minimal communication may be better than none at all. However, care should be taken to understand the social contract between the child and the patient. A particularly sensitive child may wish to protect the patient's dignity, not understanding that the provider–patient relationship relies strongly on honesty. Alternatively, a patient may not be comfortable communicating through a child of the opposite gender, thus leading to more confusion and an underreporting of symptoms. Attention to non-verbal communication becomes particularly important when children are being used as translators.

Promote health
Good nutrition and exercise, and also other lifestyle-related changes such as smoking cessation, are the cornerstones of successful ageing for all patients. Cultural differences in the perception of what is a good diet[51–54] or the proper amount or form of exercise[20,55,56] may be difficult to address, but it will be worth the effort. Lack of physical activity, combined with poor dietary habits, contributes to increased obesity in older persons. Regular exercise and

increased aerobic fitness are associated with a decrease in all-cause mortality and morbidity and are proven to reduce disease and disability and improve quality of life in older persons.

Resources

Health Literacy: http://healthlit.fcm.arizona.edu[3]
Low or inadequate health literacy is a powerful barrier to good health. An excellent resource on health literacy and older adults is readily available.[57] It is an interactive web-based module on health literacy and provides ready access to external special reports, including research projects on older adults and health literacy, assessment instruments to be used in daily practice and other resources, and can be accessed at http://healthlit.fcm.arizona.edu.[3]

Cultural competence in health care

Cultural sensitivity is a powerful strategy that health care providers can use to help reduce the negative impact of cultural differences on health outcomes. The following is a partial list of web-based resources that may be useful. A more complete list can be accessed through search engines using keywords such as Cultural Diversity, Cultural Competence, Explanatory Model, Health Promotion Programmes and Disease Self-Management.

Diversity Rx: http://www.diversityrx.org[58]
This website promotes language and cultural competence to improve the quality of health care for minority, immigrant and ethnically diverse communities. It describes how language and culture affect the delivery of quality services to ethnically diverse populations and provides resources to enable providers to learn about language and cultural competence in health care, design better programmes and policies and network with colleagues and experts. It also provides information on working with interpreters and gives examples of model programmes.

Health Research and Educational Trust Disparities Toolkit: http://www.hretdisparities.org[59]
This web-based toolkit provides guidance on how to collect patient race, ethnicity and primary language data.[60] The free toolkit provides users with resources on how to collect data from patients, how to do staff training and how to address legal and privacy concerns. The toolkit identifies the patient's preferred method of communication, any potential language barriers and the patient's culture. With this information, the provider can enlist any outside assistance needed to ensure proper patient–provider communication. The toolkit is specifically designed to be useful for educating and informing staff about the importance of data collection, how to implement a framework to collect race, ethnicity and primary language data and ultimately how to use these data to improve quality of care for all populations.

EthnoMed: http://www.Ethnomed.org[61]
This website focuses on information about cultural beliefs, medical issues and other related issues pertinent to the health care of recent immigrants to Seattle, WA or to other parts of the United States, many of whom are refugees fleeing war-torn parts of the world. It offers videos in many languages on basic medical history taking with interpreters. Hyperlinks on this site may be useful when provider and patient languages differ. In response to recent earthquake activity worldwide, it has a number of resources that may be useful to international disaster relief workers. An interesting recent addition is a video on culturally competent care in mental health. It has also posted an article on Ethiopian Traditional and Herbal Medications and Their Interactions with Conventional Drugs.[62] The herbs described are used commonly in many world cuisines.

Health promotion programmes

MOVE!: http://www.move.va.gov/[63]
MOVE! is a national weight management programme designed by the Department of Veterans Affairs (VA). This programme is designed to help Veterans lose weight, keep it off and improve their health. The entire programme, from philosophy to handouts, from motivational messages to references, can be found on the Internet and is free. The website has sections for both patients and providers in English and in Spanish. There is a simply stated patient recruitment message about why this programme in important to health and well-being, followed by questionnaires to help patients determine their degree of readiness to participate in the programme. Multiple handouts address barriers that patients may face, such as depression, lack of time and boredom. These handouts offer solutions to those barriers.

There are instructions to providers about how to administer the patient questionnaire and how to run successful group sessions. Reference tools are well labelled and accessible and include discipline-specific information on such topics as nutrition, physical activity, medications and surgery. This programme was originally designed to be promoted by providers to the patients and was so successful that the top administrators of the VA promoted it to all of the employees of the VA nationwide. Now one more layer of promotion has been added that would serve as a model for worldwide success. This programme has been so successful that Michelle Obama, First Lady of the United States, has become a spokesperson for the programme to be used to encourage obese children to be more active and increase their fitness levels.

CDSMP: http://patienteducation.stanford.edu/programs/cdsmp.html[64]

The Chronic Disease Self-Management Program developed at Stanford University is a workshop given 2.5 hours, once per week, for 6 weeks, in community settings such as senior centres, churches, libraries and hospitals. People with different chronic health problems attend together. Workshops are facilitated by two trained leaders, one or both of whom are non-health professionals with a chronic disease themselves. Subjects covered include (1) techniques to deal with problems such as frustration, fatigue, pain and isolation, (2) appropriate exercise for maintaining and improving strength, flexibility and endurance, (3) appropriate use of medications, (4) communicating effectively with family, friends and health professionals, (5) nutrition, and (6) how to evaluate new treatments.

It is the process in which the programme is taught that makes it effective. Classes are highly participative, where mutual support and success build the participants' confidence in their ability to manage their health and maintain active and fulfilling lives. Each participant in the workshop receives a copy of the companion book, *Living a Healthy Life with Chronic Conditions*, 3rd edition, and an audio relaxation tape, *Time for Healing*.

The CDSMP *Leader's Manual* is available in Arabic, Bengali, Chinese, Dutch, German, Hindi, Italian, Japanese, Korean, Norwegian, Somali, Turkish, Vietnamese and Welsh.

Key points

- Individuals with limited health literacy have less health knowledge, worse self-management skills, lower use of preventive services, higher hospitalization rates and more premature mortality than individuals with adequate health literacy.
- Medicine is a culture that is not understood by, and often intimidates, patients.
- Common areas of cultural conflict between provider and patient that negatively affect health care delivery include misunderstandings about the role of the family in the care of the patient, lack of common verbal and non-verbal communication styles, misconceptions about cultural norms and ageism by both the patient and the provider.
- Health literacy in older adults can be improved by using written material that is in the primary language of patient, is written at the sixth grade level, uses pictures and illustration, is age appropriate and presents a limited amount of information.
- Health literacy in older adults can be improved using auditory material that is in the patient's primary language, is spoken slowly and is delivered one-on-one by a trusted individual.
- There are many resources available on the Internet to assist with overcoming language barriers and developing culturally appropriate health promotion programmes.

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PART 2

Medicine and Prescribing in Old Age

CHAPTER 12

Preventive geriatrics

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Introduction

Preventive geriatrics is not an oxymoron. It is, however, a challenging area of medicine for many reasons. (1) How can guidelines for prevention take into account the variability seen among older persons? (2) How can preventive geriatrics balance the dichotomy between the treatment of populations and the treatment of the individual? (3) How can clinicians handle the unclear areas or 'grey zones' of preventive geriatrics? (4) Does early detection or case finding equate with better outcomes?

To deal with these questions, this chapter presents a model of preventive geriatrics called the *Health Maintenance Clinical Glidepath*, which is primarily for office-based practices. It addresses screening for geriatric specific areas (e.g. cognition, gait and balance) and also screening for common medical illnesses and diseases (e.g. certain cancers, heart disease).

Background

Prevention in medicine has traditionally been divided into primary, secondary and tertiary prevention. Primary prevention is the prevention of disease before it actually starts.

The traditional definition of secondary prevention is the detection of disease at an early stage. This can be detection of asymptomatic disease by screening tests or identification of unreported problems by case finding. The following caution needs to be added to the definition. Detection should only be done if detection is likely to improve outcomes such as mortality, morbidity, function or quality of life. The priority and importance of outcomes need to be made based on patient preference.

Tertiary screening, using a comprehensive geriatric assessment approach, allows for identification and intervention of established health conditions such as cognitive impairment, gait and balance disorders, malnutrition and urinary incontinence. The goal of the intervention would be to prevent or minimize a patient's functional decline in order to maintain their independent lifestyle, since functional decline and loss of independence are not inevitable consequences of ageing.

The Health Maintenance Clinical Glidepath

The Health Maintenance Clinical Glidepath answers the first two questions above and addresses the limitations of two types of clinical decision-making tools: practice guidelines and evidence-based medicine (EBM). Although practice guidelines and EBM have been important in raising the standards of healthcare in the past decade, their use in preventive geriatrics is limited. Many guidelines do not include older age groups and, if they do, they are no more specific than 'over 65 years of age'. EBM emphasizes outcomes of populations, whereas clinical practice emphasizes the outcome of the individual. One of the limitations of EBM is the discrepancy between patients in the EBM studies and in clinical practice. For example, many randomized controlled trials of medication interventions for common diseases such as congestive heart failure and osteoporosis exclude patients who are frail, demented or at the end of life.

The older we get, the more unique we become. Chronological age does not equate with physiological or functional age. Guidelines for preventive geriatrics need to take this into account. One approach is to use life expectancy and functional status to help delineate categories of older persons that are more useful than those based on chronological age. Overall health status is a good predictor of life expectancy compared with age alone and functional capacity among older persons has been found to be a predictor of mortality. Four categories can be used to help guide

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decisions about preventive measures. Although overlap exists and functional status may fluctuate, Gillick proposed the following: Robust (life expectancy of >5 years and functionally independent); Frail (life expectancy of <5e years and significant functional impairment); Moderately Demented (life expectancy 2–10 years and may or may not be functionally impaired); and End of Life (usually a life expectancy of <2 years).[1]

Preventive geriatrics requires making decisions. Healthcare decisions are complex, involving society, healthcare workers and patients. Guidelines for preventive geriatrics need to take into account the following practice principles: (1) patients' expectations and needs, including quality of life, satisfaction and reassurance; (2) physicians' need for diagnostic certainty; (3) physicians' comfort with risk taking and concerns about malpractice; (4) the need for cost-effective medical care; (5) variations in practice patterns, particularly with regard to subspecialty care; and (6) the practical realities of running a practice.[2]

Healthcare decisions are not black and white. Thus, four levels of recommendation were developed to allow for decisions to be made on a 'graded' rather than an 'all or nothing' basis and to allow for better patient involvement in decision-making. The four levels are also based, when available, on the strength or weakness of EBM that exists or does not exist. The four levels are 'Do', 'Discuss', 'Consider' and '* * * *'. 'Do' reflects the strongest recommendation. 'Discuss' reflects a recommendation that the physician discusses the risk–benefit of the decision with the patient. 'Consider' reflects a recommendation that the physician gives consideration, but does not necessarily need to discuss the decision with the patient. '* * * *' reflects that a particular evaluation or management measure is not recommended, based on these principles.

Table 12.1 is a shortened version of the original Health Maintenance Clinical Glidepath which details the recommendations for each area of prevention and for each category of Robust, Frail, Moderately Demented and End of Life. It will be noted in the following sections whether recommendations are based on organizational guidelines, EBM or expert consensus. All areas of the Glidepath underwent a Delphi process.[3]

Office visits

Although there is no direct evidence available on how often Robust elderly versus Frail or Moderately Demented elderly need office visits, because other screening procedures need to be done, the minimum frequency should be once per year. 'Do as needed' is recommended for elderly at the End of Life because of potential limitations or inability on the part of the patient to get to the office.

Blood pressure (BP) including orthostatic measurements

Performing BP measurements in all groups is recommended at each visit. Although this pertains to screening for hypertension in all four categories, it also pertains to hypotension (and associated symptoms) in the Frail, Moderately Demented and End of Life categories. Recommendations for hypertension screening are based on organizational guidelines. Although most organizations agree on the importance of screening for hypertension, they do not agree on how often. For example, the recommendations of the American College of Physicians (ACP) for BP screening for adults range from every 1–2 years to every 2–5 years for normotensive patients. The Seventh Report of the Joint National Committee for Hypertension (JNC 7) and The United States Preventative Services Task Force (USPSTF)[4] recommend BP screening for normotensive patients every 1–2 years and yearly for prehypertensive patients.[5] Note that these organizations do not take into account extreme ages of the elderly (for example, the difference between an 85-year-old and a 65-year-old person). They also set the upper limits of normal fairly low compared with more geriatric-oriented groups. The Assessing Care of Vulnerable Elders (ACOVE) Project recommends screening for systolic hypertension begin at a BP >160 mmHg.

Screening for orthostatic hypotension (OH) is based on evidence that OH is prevalent among older patients (13–30%) and that there is an association between OH and adverse outcomes. JNC 7 recommends screening all patients treated for hypertension for orthostatic hypotension, but the frequency is not specified.

Although no studies have been carried out to show improved outcomes if this screening is done, the cost and risk of the intervention are low enough that postural blood pressure measurements are recommended.

Weight

Weight loss in older patients is associated with increased mortality, morbidity and other unfavourable outcomes (e.g. loss of muscle mass, decreased muscle strength, altered immune function, decreased wound healing). The data on the benefit and outcome of nutrition management are somewhat controversial, but mostly positive. Oral nutritional supplement was shown to improve weight in nursing-home elderly, supplementation was shown to improve weight and reduce falls in frail elderly living in the community and dietary supplementation led to moderate weight gain and improvements in general well-being in homebound elderly.[6–8] A meta-analysis concluded that oral nutritional supplements can improve nutritional status and seem to reduce mortality and complications for undernourished elderly patients in the hospital. Current evidence does not

Table 12.1 The Health Maintenance Clinical Glidepath[a].

Item	Robust elderly Life expectancy >5 years and functionally independent	Frail Life expectancy <5 years or significant functional impairment	Moderately demented Life expectancy 2–10 years	End of life Life expectancy <2 years and functionally non-independent
Office visits	Do 2 times/year	Do 1–4 times/year	Do 1–4 times/year	Do as needed
Blood pressure including orthostatics	Do each visit	Do each visit	Do each visit	Do each visit
Weight	Do each visit. If loss of >5 lb/year perform MNA	Do each visit. If loss of >5 lb/year perform MNA	Do each visit. If loss of >5 lb/year perform MNA	* * * *
Height	Do each visit	Do yearly	* * * *	* * * *
Pain assessment	Do each visit	Do each visit	Do each visit	Do each visit
Medication review including OTCs and herbal medicines	Do each visit	Do each visit	Do each visit	Do each visit
Lifestyle education (exercise, smoking cessation, alcohol and injury prevention)	Do each visit	Do each visit	Discuss periodically with caregiver	* * * *
Maintain awareness of elder abuse	Do each visit	Do each visit	Do each visit	Do each visit
Assess ADLs and IADLs	Do yearly	Do yearly	Do each visit	Do each visit
Visual acuity testing	Consider yearly	Consider yearly	Consider yearly	* * * *
Auditory testing	Consider yearly	Consider yearly	Consider yearly	* * * *
Ask about urinary incontinence	Do yearly	Do yearly	Do yearly	Do yearly
Males: ask about erectile dysfunction and ADAM screen for hypogonadism	Do yearly	Do yearly	Consider yearly	* * * *
Cognitive screening	Do initially; do if symptomatic[b]	Do initially; do if symptomatic	Do initially	Consider if symptomatic
Depression screening	Do initially; do if symptomatic	Do initially; do if symptomatic	Do initially; do if symptomatic	Do initially; do if symptomatic
Screening for gait and balance	Do initially; Do if symptomatic	Do initially; Do if symptomatic	Do initially; Do if symptomatic	Do if symptomatic
Advance directives	Do yearly and as needed	Do yearly and as needed	Do yearly and as needed	Do yearly and as needed
Influenza vaccine	Do yearly	Do yearly	Do yearly	Do yearly
Pneumococcal vaccine	Do once; consider repeat every 6 years for patients with chronic diseases	Do once	Do once	Consider vaccination once
Tetanus	Do primary series if not vaccinated before and booster every 10 years	Do primary series if not vaccinated before	Do primary series if not vaccinated before	* * * *
Zostavax	Do once	Do once	Do once	Consider
Breast examination	Do yearly	Do yearly	Do yearly	* * * *
Mammography	Do every 1–2 years up to age 80 years	Consider every 1–2 years up to age 75 years	Consider every 1–2 years up to age 70 years	* * * *
Pap smear	Consider 1–3 pap smears if patient has never had one	* * * *	* * * *	* * * *
Faecal occult blood test	Do yearly	Consider yearly	Consider yearly	* * * *
Colonoscopy	Consider every 10 years	* * * *	* * * *	* * * *
PSA	Discuss pros and cons with patient	Discuss pros and cons with patient	Discuss pros and cons with caregiver	* * * *

(*continued overleaf*)

Table 12.1 (*continued*)[a].

Item	Robust elderly Life expectancy >5 years and functionally independent	Frail Life expectancy <5 years or significant functional impairment	Moderately demented Life expectancy 2–10 years	End of life Life expectancy <2 years and functionally non-independent
Osteoporosis	Do at least once; consider every 2 years	Do at least once every 2 years	Do at least once	* * * *
Cholesterol screening	Consider screening for patients aged 65–75 years if they have additional risk factors (e.g. smoking, diabetes, hypertension)	Consider screening for patients aged 65–75 years if they have additional risk factors (e.g. smoking, diabetes, hypertension)	* * * *	* * * *
TSH	Do every 2 years	Do every 2 years	Do every 3 years	Consider
Fasting blood glucose	Do if symptomatic or every 3 years if the patient has risk factors	Do if symptomatic or every 3 years if the patient has risk factors	Do if symptomatic or every 3 years if the patient has risk factors	Consider if symptomatic
Sleep apnea	Do yearly	Do yearly	* * * *	* * * *

[a]MNA, Mini-Nutritional Assessment; OTC, over-the-counter; ADLs, activities of daily living; IADLs, instrumental activities of daily living; ADAM, androgen deficiency in adult males; PSA, prostate-specific antigen; TSH, thyroid-stimulating hormone.
[b]The term 'symptomatic' refers to any complaint given by the patient or caregiver or any problem observed/elicited by the clinician.

support routine supplementation for older people at home or for well -nourished older persons in any setting.[9]

Since screening for weight loss is very low cost and low risk and the benefits of intervention are mostly positive, it should be done for patients in all categories except End of Life. Outpatient screening of unintentional weight loss of 10% or greater in 1 year is indicative of significant malnutrition. Utilizing a validated screening tool, such as the Mini-Nutritional Assessment (MNA), can identify patients who are malnourished or at risk for malnutrition.[10]

Height

Since measuring height is a low-cost screening intervention and as bone loss occurs height may decrease, it may be an effective and economical method to identify early osteoporosis of the spine for Robust and Frail elderly. One study showed a significant association with historical height loss of 1.5 cm and vertebral fractures.[11]

Pain

Pain should now be considered the fifth vital sign and should be assessed at every visit for patients in all categories. Use of Likert scales (e.g. 1–10) or pictorial scale (e.g. facial expressions) can be useful to quantify pain. Even patients with dementia can be evaluated for pain, using such tools as the CNA Pain Assessment Tool (CPAT) and the Pain Assessment in Advanced Dementia Scale (PAINAD-G).[12,13]

Medication review including over-the-counter (OTC) and herbal medicines

The risk of adverse drug events, poor compliance and drug–drug interactions, and even the risk of hospitalization, are most associated with number of drugs, while underlying comorbidities and to some extent age contribute to this risk.[14,15] Patients should maintain an up-to-date medication list including OTC and herbal preparations, to bring in at each office visit or hospitalization. Medication reviews should be performed for patients in all four categories at each office visit, to assess for duplication, drug–drug or drug–disease interactions, adherence, affordability and side effects.

Lifestyle education

Recommendations about areas of lifestyle education in general apply mainly to the Robust and Frail elderly,

with a lower level of recommendation for the Moderately Demented elderly. Activity level should be queried because a low level of activity is a significant predictor of mortality among older adults.[16] In robust elderly, physical activity plays an important role in prevention and reduction of mortality and treatment of various chronic and disabling conditions (e.g. obesity, cardiovascular disease, stroke, diabetes mellitus type 2, hypertension, depression, osteoporosis, osteoarthritis, cognitive decline). Frail elderly undergoing randomized trials of exercise experienced fewer falls, injuries and healthcare utilization. Although the USPSTF does not recommend behavioural counselling of elderly patients by primary care physicians to promote increased physical activity, other professional organizations, such as the ACP, American Heart Association (AHA) and American College of Sports Medicine (ACSM) do support exercise promotion in the elderly. Specific recommended exercises fall into four categories: aerobic, muscle strengthening, flexibility activities and balance training.

Physicians should ask patients about smoking and should clearly and directly advise all smokers to quit. Patients who want to quit should be assisted with self-help materials, encouraged to set a quit date, be referred for behavioural therapy or be advised to try OTC or prescription medications.

Alcohol abuse can initially be screened for by asking what quantity a patient consumes on a regular basis. Men who consume more than four drinks per day and women who consume more than two drinks per day are at risk of alcohol-related problems.[17] A more thorough assessment should include screening tools such as the CAGE questionnaire, MAST or AUDIT. Of these three, the CAGE questionnaire has the best sensitivity and specificity for diagnosing alcohol dependence.[18] Both the USPSTF and the American Geriatrics Society (AGS) recommend that primary care providers screen their older patents for alcohol misuse.

Areas of education for injury prevention include the use car seat belts, alcohol-related risks in relation to driving, home environmental hazards to reduce falls and the restriction of access to firearms and driving with depressed and cognitively impaired patients.[5]

Maintain awareness of elder abuse

Physicians and other healthcare professionals should maintain awareness at all times for patients in all categories. A review of elder abuse screening and assessment instruments have shown that older adults were unlikely to report episodes of elder mistreatment and identification of 70% or more of elder mistreatment comes from third-party observers.[19] Healthcare providers should consider referral to a social service agency for evaluation of mistreatment if elderly patients present with unexplained contusions, burns, bite marks, genital or rectal trauma, pressure ulcers and a BMI of less than 17.5%.

The term 'awareness' is used because no particular standardized evaluation tool for elder abuse has been shown to be better than others.[20]

Assess ADLs and IADLs

Prevention of functional decline is one of the hallmarks of geriatric care. Loss of function among older persons is associated with long-term care placement, morbidity and mortality. Thus, although there is no direct evidence on how often to screen older patients in each of the four categories for functional change, given the importance of this health parameter it is recommended for patients in all categories at the intervals as noted in Table 12.1.

Two commonly used measurements of function are Activities of Daily Living (ADLs) (bathing, dressing, toileting, transferring, continence, feeding) and Instrumental Activities of Daily Living (IADLs) (telephone, shopping, food preparation, housekeeping, transportation in the community, taking medications, handling finances).

Visual acuity and auditory testing

Although both of these are an accepted part of the comprehensive geriatric assessment (CGA), the level of recommendation for testing these areas is 'consider' for patients in all categories. Based on a review of vision screening studies, direct evidence of vision screening in asymptomatic older adults in primary care settings found no effect in improving visual acuity or other clinical outcomes.[21] The USPSTF concluded that evidence is insufficient to determine whether screening older adults for visual impairment improves functional outcomes. However, due to improved treatment of various chronic eye diseases, the National Eye Institute, the American Optometric Association and the American Academy of Ophthalmology do recommend routine comprehensive eye examinations in asymptomatic patients performed by optometrists or ophthalmologists every 1–2 years.

Likewise, although there is evidence that decreased hearing is common and associated with negative outcomes, there is a lack of EBM that screening will improve outcomes.[22] However, use of hearing aids or surgical intervention has a positive effect on quality of life. The ACOVE authors suggest an annual hearing screening by either questionnaire or hand-held audiometry.

Ask about urinary incontinence

The level of recommendation here is the highest for all categories because urinary incontinence is common among women and may occur in men, is easy to screen for (usually one to two questions) and multiple effective treatments are available.

Males: screen for erectile dysfunction (ED) and hypogonadism

It is recommended that this be done for males in robust and frail categories, but should only be considered in males with moderate (not severe) dementia. ED is common, with multiple treatments available.

Male hypogonadism is also common and is associated with muscle weakness and osteoporosis. The ADAM (Androgen Deficiency in Aging Males) screen for hypogonadism has high sensitivity and adequate specificity (see Chapter 111 for details.)

Cognitive screening

Screening for cognitive impairment is part of a CGA and should be done at initial visits for patients in all categories, except for those at End of Life, where it should be considered. The Mini-Mental State examination is a commonly used screening tool, but may have limited utility if the cut-off score is set too high.[23] For elderly with high education levels, the Saint Louis University Mental Status (SLUMS) examination, along with other screening tests, may be used.[24]

Depression screening

Depression screening should be carried out at initial visits for patients in all categories A systematic review concluded that screening for depression can improve outcomes, particularly when screening is coupled with system changes that help ensure adequate treatment and follow-up.[25]

Screening for depression is part of a CGA. There is no strong evidence for one particular screening instrument for depression. The Geriatric Depression Scale (GDS) may be one of the easiest to administer.[26] However, the GDS does not maintain its validity for patients with dementia and the Cornell scale (a 19-item clinician-administered instrument) is recommended.[27]

Screening for gait and balance

The evidence to screen for gait and balance problems at initial visits in all categories except at End of Life is based on the fact that falls are associated with decreased function, increased nursing home admission and increased morbidity and mortality in populations similar to patients in these categories. One of the best 'screeners' for gait and balance problems is to ask patients if they have fallen. The 'Get Up and Go Test' may quantify functional mobility in addition to testing balance and may also be useful in following clinical change over time.[28,29]

Advance directives

Although the evidence is not strong that advance directives make a difference in outcomes (e.g. one study showed that systematic implementation of a programme to increase use of advance directives reduced the utilization of healthcare services without affecting satisfaction or mortality),[30] there are ways to increase discussions and completions of advance directives.[31] Clinicians should take care to assure that underlying depression does not underlie patient preferences or decisions.

Advance directives are especially important for patients in the Frail, Moderately Demented and End of Life categories.

Influenza vaccine

This should be done yearly for patients in all categories. More than 90% of the deaths attributed to pneumonia and influenza during epidemics occurred among persons aged 65 years and older. Influenza vaccination in the elderly has been shown to reduce hospitalization rates, to be cost-effective and to reduce influenza-associated mortality. In the nursing home, although vaccination is only 40% effective in preventing clinical illness, it is more effective in preventing pneumonia, hospitalization and death. Vaccinating more than 80% of nursing home residents has been shown to prevent influenza outbreaks.[32,33]

Pneumococcal vaccine

The recommendations about pneumococcal vaccine are based on some evidence and based on probable life expectancy in various categories. Although pneumococcal vaccination increases antibody levels in older adults to a lesser extent than younger adults and levels decrease more rapidly in the elderly, vaccination has been shown to be effective in reducing the incidence of pneumococcal bacteraemia in older, high-risk patients who have good antibody response to the vaccine.

Most organizations recommend one dose of the 23-valent pneumococcal vaccine to be given for all adults over age 65 years. Older patients who received the earlier 14-valent vaccine should be revaccinated with the 23-valent vaccine if they fall into any of those two groups. If patients have had the 23-valent vaccination before age 65 years, the recommendations for revaccination are controversial.[5] The ACP

reports that there are currently insufficient data on repeated revaccination every 6 years in healthy elderly and most other organizations do not provide specific recommendations for revaccination. However, since older patients with chronic diseases may occasionally be 'Robust' for other reasons, clinicians should '*consider* repeating' every 6 years.

Tetanus

Recommendations regarding adult tetanus/diphtheria vaccination do not vary for older persons from those for younger adults. Over half of the cases of tetanus occur in persons aged 60 years or older. All adults should complete a primary series of tetanus/diphtheria toxoid (Td). If an individual had an incomplete series or an uncertain history, it is recommended that the entire primary series be given. Primary series for adults consists of 0.5 ml of Td intramuscularly as the initial dose and at 2 and 6 months later. Booster doses need to be given every 10 years.[5,34]

Zostavax

Reactivation of latent varicella zoster virus results in a localized eruption known as herpes zoster (shingles). Its incidence increases with age, occurring in up to half of individuals age 85 years or older. Postherpetic neuralgia is a potentially devastating complication, occurring in more than 40% of individuals older than 60 years.[35] In 2006, the FDA approved the use of Zostavax in patients age 60 years or older for prevention of recurrent herpes zoster infection. The Advisory Committee on Immunization Practices (ACIP) recommends a one-time dose of Zostavax for immunocompetent adults age 60 years or older regardless of known prior herpes zoster infection.

Breast cancer screening

There is no evidence for or against the clinician recommending self-examination or the clinician doing the clinical breast examination. Breast self-examination may allow women to detect lesions or breast cancers not seen on mammography or those that develop in between mammography or clinical breast examinations. Clinicians performing breast examinations may find lesions or breast cancers not detected on mammography. Breast examinations should be performed yearly in all categories except for those in the end of life category.

Mammography is the mainstay of breast cancer screening. Research has shown mammography to be effective up to age 80 years.[36] There is lack of agreement among organizations regarding screening with mammography. The American Cancer Society (ACS) recommends yearly mammography in older adults provided that a women is in good health. There are few studies that describe women's decision-making to stop mammography. It appears that some women and their health providers, recognizing that the expected benefit of early detection declines with remaining life expectancy, consciously decide to discontinue screening following a serious health event.[37] The USPSTF recommends biennial screening mammography for women up to age 74 years.

Cervical cancer screening

The low levels of recommendation for Robust ('consider') and 'Don't Do' for the other categories are based on lack of evidence and organizational recommendations. The ACP and the USPSTF recommend no further Papanicolaou (pap) smears for women over age 65 years who have had previous regular screening with consistently normal results. The AGS position statement says that regular pap smear screening at 1–3 year intervals until at least the age of 70 years seems reasonable. Beyond that age, there is little evidence for or against screening women who have been regularly screened in previous years. An older woman of any age who has never had a pap smear may be screened with at least two negative pap smears 1 year apart. The ACS and AGS both recommend that women 70 years and older who have tested positive for HPV DNA should continue screening at the discretion of their healthcare provider.

Colon cancer screening

Regular screening or testing is one of the most effective means of preventing colorectal cancer. This is because most polyps or growths can be found and removed before they have the chance to turn into cancer. The clinician's choice of screening procedure for colon cancer depends on extrinsic factors (e.g. transportation, availability of a gastroenterologist, the patient's willingness to do one procedure over the other and the patient's health status). It is recommended that clinicians consider ordering screening colonoscopies for their robust patients based on current guidelines and based on the number of years it takes for polyps to turn into cancer. Primary care physicians may choose to limit screening in frail individuals or patients with dementia.

The recommendations on the type and frequency of screening procedures vary among different organizations. The USPSTF supports the use of either screening colonoscopy every 10 years, annual screening with a sensitive faecal occult-blood testing (FOBT) or flexible sigmoidoscopy every 5 years with a mid-interval sensitive FBOT. The recommended age of screening is from 50 to 75 years. The ACS lists the following options for colon cancer screening: flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, double-contrast barium enema

every 5 years, virtual colonoscopy (CTC) every 5 years or annual three-sample FBOT. Colonoscopy is a more thorough examination and is the preferred option for screening. Virtual colonoscopy (CTC) is the newest type of screening and should be reserved for patients who cannot undergo a colonoscopy. The ACS does not list an upper age limit on screening.

Prostate cancer screening

The biggest controversy in prostate screening is that some prostate cancers grow slowly and would never cause any problems. Because of an elevated PSA, men may be diagnosed and treated for prostate cancer with either surgery or radiation for lesions that would not cause symptoms or lead to their death. These treatments have side effects that can seriously affect a man's quality of life. No major scientific or medical organization, including the ACS, American Urologic Association (AUA), USPSTF, American Academy of Family Physicians and the American college of Preventive Medicine, support routine testing for prostate cancer at this time. The National Comprehensive Cancer Network (NCCN) guidelines focus on men at an increased risk for developing prostate cancer due especially to family history and race. These organizations emphasize the need for healthcare professionals to discuss, with the male patients, the possible benefits, side effects and questions about early prostate cancer detection. Therefore men, at least 50 years old or younger if at higher risk, can make informed decisions taking into account their own situations.

Osteoporosis

The recommendation to screen at least once for patients in all categories except End of Life is based on studies that show inadequate rates of diagnosis and treatment. However, there is lack of evidence to show that mass screening of all elderly women and men will be cost-effective or improve outcomes related to osteoporosis.[38]

Dual-energy X-ray absorptiometry (DXA) is the current gold standard test for diagnosing osteoporosis in people without a known osteoporotic fracture. It is, however, an imperfect test, diagnosing osteoporosis in less than half of people who progress to have an osteoporotic fracture.[39] Other screening methods have been evaluated to improve the diagnostic accuracy of osteoporosis. These include the WHO fracture risk algorithm (FRAX), which computes the 10 year probability of fractures in men and women from clinical risk fractures: age, gender, previous fracture, femoral neck BMD, body mass index, prior corticosteroid use, history of rheumatoid arthritis, parental history of hip fracture and current smoking and alcohol use.[38,39] The osteoporosis self-assessment screening tool (OST) and calcaneal ultrasound are also both being evaluated in men and women to determine their potential role in better diagnosis of osteoporosis. The USPSTF recommends osteoporosis screening using DXA for routine screening of women at age 65 years and for women at age 60 years with risk factors for osteoporosis. The frequency of screening and the age at which to stop screening are not known. In addition to women, the ACP recommends periodic assessment of men for risk factors for osteoporosis (low body weight, physical inactivity, chronic glucocorticoid use, previous fragility fracture and hypogonadism) and DXA scanning for men at increased risk and who are candidates for drug treatment.

Cholesterol screening

The reason for a low-level recommendation (i.e. 'consider') and a targeted approach (only for the robust and frail with additional risk factors) for cholesterol screening is because there is limited evidence about primary prevention of coronary heart disease using drugs in older populations. However, there are recommendations by organizations for secondary prevention of coronary heart disease in the elderly. The USPSTF does recommend screening individuals age 65 years or older with coronary risk factors because studies have shown a reduction in coronary events on treating patient's with statins compared with placebo. The National Cholesterol Educational Program reaffirms the position that older persons, who are at higher risk and in otherwise good health, are candidates for cholesterol-lowering therapy. The decision to treat should also be based on coexisting disease, social and economic considerations and functional age. There is no upper limit for age of screening and treatment for lipid disorders in the elderly. The recommendations for the frequency of screening are not known.

Thyroid-stimulating hormone (TSH)

TSH screening of all older adults is not currently recommended by the USPSTF on the basis of lack of data. It does recommend screening of symptomatic patients. The ACP suggests office screening of women older than 50 years may be indicated. However, the evidence for treating subclinical thyroid dysfunction is inconclusive.[40] The American Thyroid Association issued guidelines which recommend measuring TSH level starting at age 35 years and every 5 years thereafter. Hypothyroidism may not be associated with adverse outcomes in the oldest individuals when detected by screening alone. A prospective study involving individuals aged 85 years or older did not show an association of elevated TSH levels with reduction in cognitive function, mood or performance of ADLs. Higher TSH

levels were associated with lower all-cause and cardiovascular mortality.[41] Many geriatricians advocate screening high-risk populations such as nursing home populations, frail elderly and patients with dementia.[42] The sensitive TSH assay is probably the screening test of choice.

Fasting blood glucose

This recommendation is based on organizational recommendations only. Although the USPSTF recommends against routine screening for diabetes in asymptomatic individuals, it does endorse screening for patients with a blood pressure of 135/80 or greater. The American Diabetes Association has recommended fasting plasma glucose measurement every 3 years in adults with one or more of a long list of risk factors. It also recommended yearly fasting glucose measurements in patients with pre-diabetes (fasting blood sugar between 100 and 125 mg dl^{-1} or 2 h postprandial blood sugar between 140 and 199 mg dl^{-1}).

Sleep apnea

Because of the low cost of screening (in the form of asking about symptoms of sleep apnea during the routine history and physical or to use a screening questionnaire tool such as the Epworth Sleepiness Scale)[43] and the potential to miss this diagnosis among older patients, it is recommended for robust and frail elderly. Two studies have shown some benefit of treatment of sleep apnea in patients with heart failure and stroke.[44,45]

Abdominal aortic aneurysm

Performing a one-time screening for abdominal aortic aneurysm with abdominal ultrasound has been shown to reduce mortality in men. However, no benefit was shown for similar screening in women.[46,47] The USPSTF and the AHA currently recommend screening in men aged 65–75 years who have ever smoked. They do not recommend screening in women. There is no recommendation for screening men who have never smoked except in individuals who had a first-degree relative who underwent an abdominal aneurysm repair.[5]

Key points

- Health promotion and preventive medicine are key to good outcomes
- Older persons with different levels of function require different approaches
- Vaccinations remain important in older people

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CHAPTER 13

Polypharmacy

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Introduction

Geriatric patients are frequently prescribed multiple drugs in complex dosage schedules. In some instances, this is justified because of the presence of multiple chronic medical conditions, the proven efficacy of an increasing number of drugs for these conditions and practice guidelines that recommend their use. In many instances, however, complex drug regimens are unnecessary; they are costly and predispose to non-compliance and adverse drug reactions. Many older patients are prescribed multiple medications, take over-the-counter drugs and are then prescribed additional drugs to treat the side effects of medications they are already taking. Taking over-the-counter drugs, such as vitamins, often leads to non-compliance with therapeutically appropriate drugs.

Although persons aged 65 years and older comprise only about 12% of the US population, they consume one-third of all prescribed drugs and more than half of over-the-counter medicines. Overall, more than 80% of all community-dwelling elders use prescription drugs, with the average older person using between three and eight drugs and 70% of nursing home residents in the USA are receiving more than nine drugs.[1] The devastating consequences of medical errors have been clearly detailed in the book *To Err is Human* by the Institute of Medicine. Medical errors are not uncommon, leading to a number of deaths ranging between 44 000 to 98 000 at a cost of $17–29 billion per year. A Harvard study done in 51 New York hospitals involving 30 000 patients reported that 3.7% had a treatment adverse event and there was a doubling in the number of undesirable treatment effects in persons over 65 years of age. Most errors are preventable; errors of omission are as important as errors of commission.[2]

In addition to concerns about the risks of excessive and inappropriate drug prescribing, there are also concerns about the consequences of underprescribing potentially beneficial drugs. With the increasing numbers of patients surviving to older ages and comprising such a large proportion of drug use, a clear understanding of the risks, benefits and consequences of drug therapy in older patients is needed.

Pharmacokinetics

Pharmacokinetics (the study of the action of a drug in the body over time) changes with age. The physiological changes that accompany ageing alter the pharmacological processes of absorption, distribution, metabolism and elimination. The effects of these age-related changes are variable and difficult to predict. Some of these physiological changes are related solely to ageing, whereas others are most likely caused by the combined effect of age, disease and the environment. Even though increasing age is often accompanied by reductions in the physiological reserve of many organ systems, independent of the effects of disease, these changes are not uniform; substantial variability exists from individual to individual, which makes some older patients more vulnerable than others.

Of the four traditional components of pharmacokinetics – absorption, distribution, metabolism and excretion – only the last three are meaningfully affected by age. In the absence of malabsorptive syndromes, traditional oral formulation of drugs are absorbed as well in old age as in youth; indeed, the well-reported changes in gastric motility and blood flow to the gut with ageing do not appear to alter the efficiency with which medications move (mainly by passive diffusion) from the gastrointestinal tract into the systemic circulation. More important changes occur from the concurrent administration of several medications at the same time. However, some drugs commonly used for older persons require food for optimum absorption, for example, megestrol acetate which is used to stimulate appetite and weight gain has minimal absorption without food (Table 13.1).

Unlike absorption, drug distribution is affected by age in clinically meaningful ways. Serum albumin, the major

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 13.1 Relevant changes in ageing and pharmacology.

Pharmacological parameter	Age-related changes	Clinical effect
Tissue sensitivity	Alterations in: Receptor number and affinity Nuclear responses Second messenger function	Patients are more sensitive or less sensitive to a given medication
Absorption	Decrease in: Splanchnic blood flow Absorptive surface gastrointestinal motility Increased gastric pH	Minimal changes associated with ageing
Distribution	Decrease in: Total body water Serum albumin Lean body mass Increased fat	Higher concentration of drugs Longer elimination half-life of lipid-soluble drugs
Metabolism	Decreased liver blood flow and enzyme activity	Decreased biotransformation and first-pass metabolism
Excretion	Decreased renal perfusion, glomerular filtration rate and tubular secretion	Decreased renal elimination of drugs

drug-binding protein, declines in sick patients due to cytokine excess. Even in healthy patients where there is a small decline, this can substantially increase the amount of free drugs available for action. This effect is of particular relevance for highly protein-bound drugs, especially when they are used simultaneously and compete for protein-binding sites. In long-term care residents, diphenylhydantoin toxicity with low serum levels can occur because the decrease in albumin. Hence measurement of a free dilantin level can be essential in these situations.

The relative increase in body fat and decrease in lean body mass alter drug distribution, such that fat-soluble drugs distribute more widely and water-soluble drugs less widely; this fact can potentially lead the healthcare professional to the wrong decision due to misinterpretation of serum drug levels. Many assays measure the total amount of drug that is present in serum, both protein-bound and unbound (free). The unbound concentration is more clinically relevant than the total concentration because only unbound drug is pharmacologically active.[3] For a patient with hypoalbuminaemia or another deficiency in binding protein, any given serum drug level reflects a greater concentration of unbound drug than the same level would signify in a patient with normal protein-binding capacity. A hypoalbuminaemic patient with a normal total serum drug concentration may actually have an unbound drug concentration that is unacceptably high. By contrast, the same patient with a slightly lower than normal total serum concentration may have an unbound drug concentration that is in reasonable range[3] (Table 13.2).

Table 13.2 Volume of distribution for commonly used medications[a].

Decreased volume	Increased volume
Ethanol	Diazepam
Gentamicin	Oxazepam
Digoxin	Prazocin
Cimetidine	Acetaminophen
Phenytoin	Salicylates
Quinine	Tolbutamide
Theophylline	Chlordiazepoxide
Meperidine	

[a] If the volume of distribution is higher, drug levels are higher.

In evaluating serum drug levels in the older patient, it is also important to recall that the therapeutic range routinely reported in such assays may not be an accurate guide to either efficacy or toxicity in the geriatric patient. Such ranges have typically been defined in non-elderly subjects and cannot take into account pharmacodynamic differences or idiosyncratic aspects of specific agents.[4]

The other important aspect is the drug distribution, which varies considerably with age; the volume of distribution (V_d) is a virtual space in a given patient which a particular drug occupies. Age-related changes in body composition can greatly affect pharmacology by altering V_d; the elimination half-life of a drug varies with the V_d:drug clearance ratio. Thus, even if the same rate of clearance of a drug

is unchanged with age, changes in V_d can affect a drug's half-life and duration of action.

Because the total body water and lean body mass decline with increasing age, drugs that distribute in these compartments, such as antibiotics, digoxin, lithium and alcohol, may have a lower V_d and can, therefore, achieve higher concentrations from given amounts of drugs. On the other hand, drugs that distribute in body fat, such as many of the psychotropic agents, have a high V_d in geriatric patients. The larger V_d will thus cause a prolongation of the half-life unless the clearance increases proportionately, which is unlikely to happen with age.[4]

As an example of the necessary precautions that need to be implemented in elderly patients, warfarin is an excellent candidate because it has been used more often in older persons. Warfarin inhibits the four vitamin K-dependent coagulant proteins, factors II, VII, IX and X, and it is highly protein-bound (97–99%), which could be a problem in malnourished patients, metabolized in the liver and, with a half-life of 42 h, its onset of action is ~36–72 h, with a peak effect within 5–7 days.

Warfarin has been proven to be effective in prophylactic or therapeutic anticoagulation, but the risk of major bleeding with increasing levels of prothrombin time/international normalized ratio (PT/INR) is a major concern; it is increased by the presence of comorbid conditions such as heart failure, liver or kidney failure or cancer. The warfarin dose should be highly individualized and may have to be adjusted several times, based on laboratory test results depending on the target INR for the patient's condition; strict adherence to the prescribed dosage schedule is necessary and patients should be informed not to take or discontinue any other medications, except on the advice of a physician or pharmacist. Checking the pharmacogenomics[5] for all patients when initiating warfarin is recommended. An excellent algorithm for initiating warfarin treatment can be found at www.warfarindosing.org.

In elderly patients, initial doses of warfarin typically are lower and INR monitoring should be performed more frequently and because warfarin possesses numerous drug interactions, some of which increase the effects of warfarin and others that decrease its effects, caution must be observed when any drug, herbal, nutritional supplement or dietary changes are made to existing regimen of a patient receiving warfarin.

Metabolism and drug clearance

The liver represents the major site of metabolism for many medications. Hepatic transformations of drugs are categorized into phase I (preparative) and phase II (synthetic) reactions. Phase I reactions include oxidations (hydroxylation, *N*-dealkylation and sulfoxidation), reductions and hydrolyses. Phase II reactions involve conjugation of the drug molecule to glucuronides, sulfates or acetates. There is evidence of decline in phase I reactions with increasing age and that the decline is more prominent in men than in women. In contrast, the second phase of drug metabolism appears to be less affected by age. There is also evidence that the ability of environmental factors (most importantly smoking) to induce drug-metabolizing enzymes declines with age.[6]

Significant age-related declines in liver size and in liver blood flow have been described; in terms of absolute hepatic blood flow, reductions of 25–47% have been reported in persons between the ages of 25 and 90 years. This decrease is clinically important because hepatic metabolism is the rate-limiting step that determines the clearance of most metabolized drugs. This effect is especially relevant for drugs that undergo rapid hepatic metabolism (e.g. propranolol). Also, drugs that undergo extensive first-pass metabolism are likely to reach higher blood levels if hepatic blood flow is decreased.

The cytochrome P450 (CYP) system, located in the smooth endoplasmic reticulum of hepatocytes, is the main catalyst of phase I reactions. Many isoforms of CYP exist, the most important being CYP3A4, ~60% of CYP enzymes are found in the liver and the remainder are found in the intestine, kidney and brain. Many commonly prescribed medications serve as substrates for these enzyme systems. Phase 1 metabolism often undergoes a substantial decrease in activity in elderly patients as a result of illness or drug interactions; drugs that are metabolized through phase I enzymatic activity will have prolonged half-lives, but there is no easy way to predict the effects of changes in phase I metabolism in an individual patient or to adjust maintenance doses of drugs that undergo this form of metabolism[6] (Table 13.3).

In contrast, phase II hepatic metabolism involves the conjugation of drugs or their metabolites to organic substrates. The elimination of drugs that undergo phase II metabolism by conjugation is generally less altered with age. Thus, drugs that require only phase II metabolism for excretion do not have a prolonged half-life in older people.

Elimination and renal excretion

Unlike the effects of metabolism, those of ageing on renal functions are somewhat more predictable. The tendency for renal function to decline with age can affect the pharmacokinetics of several drugs (and their active metabolites) that are eliminated predominantly by the kidney. Clearance of drugs from the body occurs more slowly, their half-lives are prolonged and there is a tendency to accumulate to higher drug concentrations in the steady state (Table 13.4).

Although blood urea nitrogen (BUN) and serum levels may be useful (albeit crude) markers of renal function, it

Table 13.3 Metabolism of some drugs by the hepatic cytochrome P450 system is altered by ageing.

	Cytochrome P450				
	CYP1A2	**CYP2C9**	**CYP2C19**	**CYP2D6**	**CYP3A4**
Substrates	Olanzapine Theophylline	Phenytoin Warfarin	Diazepam Omeprazole Phenytoin	Codeine Desipramine Haloperidol Metoprolol Paroxetine Risperidone	Alprazolam Nifedipine Terfenadine Triazolam Verapamil
Inducers	Omeprazole Smoking		Rifampin		Phenytoin St John's wort
Inhibitors	Cimetidine Ciprofloxacin		Amiodarone Fluconazole		Erythromycin

Table 13.4 Medications with decreased renal excretion.

Triamterene	Atenolol
Sotalol	Amantadine
Procainamide	Ampicillin
Ranitidine	Cimetidine
Pancuronium	Cephradine
Phenobarbital	Ceftriaxone
Penicillin	Digoxin
Lithium	Furosemide
Kanamycin	Doxycycline
Hydrochlorothiazide	Gentamicin

must be remembered that each is susceptible in its own way to perturbations that can occur with ageing but have nothing to do with renal function itself. For example, BUN reflects the concentration of urea in the blood. However, the origin of much of this urea is ingested protein, so that a malnourished older patient may not consume enough nitrogen to produce an appropriate rise in BUN, even in the face of renal impairment. Similarly, creatinine is produced by muscle and if a patient has a markedly diminished muscle mass, whether because of chronic illness or any other cause, he or she may not produce enough creatinine to reflect a change in the ability of the kidney to excrete this substance. Hence over-reliance on normal-appearing BUN and creatinine in older patients can severely underestimate the degree of renal impairment. Further decrement in renal function is common in the elderly because they frequently have chronic illnesses that affect the kidney such hypertension, diabetes mellitus and atherosclerosis.

Early cross-sectional studies of renal function in ageing suggested that there is a linear decrease in renal function between young adulthood and old age, amounting on average to a reduction in glomerular filtration rate by nearly one- third. The average clearance declines by 50% from age 25 to 85 years, despite the serum concentration that in healthy adults remains unchanged. Because the serum levels tend to overestimate the actual clearance in older persons, the commonly cited equation devised by Cockcroft and Gault may be used to estimate clearance in older adults:

$$\mathrm{CrCl} = \frac{(140 - \mathrm{age}) \times \mathrm{weight(kg)}}{70 \times \mathrm{serum\ Cr}}$$

(for women, multiply by 0.85). However, it should be recognized that this equation represents a poor approximation of renal function in the old-old.

The MDRD (modification of diet in renal disease) equation is a better equation for estimating creatinine clearance in older persons. Cystatin C, which comes from the nucleus and is cleared by the kidney, is the preferred measure for estimating glomerular filtration rate in older persons.

Altered renal clearance leads to two clinically relevant consequences: (1) the half-lives of renally excreted drugs are prolonged and (2) the serum levels are increased. For drugs with large therapeutic indexes (e.g. penicillin), this is of little clinical importance; however, for drugs with a narrower therapeutic index (e.g. digoxin, cimetidine, aminoglycosides), side effects may occur in older patients if a dose reduction is not made. Thus, digoxin is the drug that most often causes side effects in the elderly, especially when doses exceed 0.125 mg per day. To define dose requirements further, therapeutic drug monitoring is useful for doses of drugs with a low therapeutic index.

A common goal of pharmacotherapy in older persons is to achieve and maintain a therapeutic steady-state serum concentration. The steady-state drug concentration is proportional to the medication dosing rate and is inversely proportional to drug clearance. This relationship has a number of important ramifications for the prescriber. Although drug clearance is a biologically determined characteristic of each patient over which the prescriber has no

control, dose and dosing interval are variables that can be modified. To prevent the excessive accumulation of a drug when its clearance is reduced, one can reduce the dose, increase the interval between doses, or both, depending on the situation.

Pharmacodynamics

A proportion of the drug or its active metabolite will eventually reach its site of action. Age-related changes at this point, that is, responsiveness to given drug concentrations (without regard to pharmacokinetic changes) are termed *pharmacodynamic changes*.

Pharmacodynamics has been less extensively studied than pharmacokinetics in older patients. Generalizability is not straightforward; the effect of age on drug sensitivity or the binding of drug to receptor sites varies with the drug studied and the response measured. These differences in sensitivity occur in the absence of marked reductions in the metabolism of the drug and its related compounds.

Older persons are often said to be more sensitive to the effects of drugs. For some drugs, this appears to be true; however, sensitivity to drug effects may decrease rather than increase with age. For example, older persons may be more sensitive to the sedative effects of given blood levels of benzodiazepines but less sensitive to the effect of drugs mediated by β-adrenergic receptors; hence the sensitivity to drug effects may either increase or decrease with age. Other possible explanations offered for these differences are alterations in second messenger function and cellular and nuclear responses.

In general, and because the response of older patients to any given medication is variable, medications should be used with caution to achieve the goal of minimizing risks. This problem could be minimized by knowing the pharmacology of the drugs prescribed, limiting the number of medications used, determining the dosage and preparation on the basis of the characteristics of each individual patient, with downward adjustment for known hepatic or renal illness, and by surveying for side effects (Table 13.5).

Table 13.5 Examples of adverse drug reactions.

Type of drug	Common adverse reaction
Aminoglycosides	Renal failure, hearing loss
Anticholinergics	Dry mouth, delirium, constipation
Narcotics	Constipation, sedation
Diuretics	Dehydration, hyponatraemia, hypokalaemia, incontinence
Sedative-hypnotics	Excessive sedation, delirium, increased risk for falls
Anti-arrhythmics	Diarrhoea, urinary retention
Antipsychotics	Delirium, sedation, extrapyramidal movements

Pharmacogenetics

This novel area of research and development in the medical sciences has been defined as the identification of differences in drug effects that have a genetic basis, but also the development of simple methods by which susceptible individuals can be recognized before the drug is administered.

It has been said that the major concern of pharmacogenetics is related to using information about how the effect of variations in the genetic makeup could affect the clinical efficacy of drugs, the required dose of drugs, the choice of the correct agent and the risk for side effects to drugs.[7]

The fundamental theory of pharmacogenetics states that genotype affects expression of genes resulting in a phenotype and the expression of genes is also modified by agents in the environment. Conversely, the expression of the gene may influence the efficacy of a drug by affecting its metabolism, availability at its site of action and by how the drug binds to its target receptors and achieves a desired pharmacological action. The rapid growth of pharmacogenetics has been helpful in terms of rapid identification and gene sequencing for drug targets, including receptors, transport proteins, ion channels and enzymes that metabolize drugs.

Currently available data on pharmacogenetic research has shown that it will be useful in the near future since the therapeutic–pharmacological approach in many chronic diseases is promising. For example, in chronic conditions or environmental exposures such as nicotine addiction, the response of smokers to drugs for smoking cessation differ according to variations in genes encoding several receptors and enzymes. Genetic variations that affect the function and availability of proteins (dopaminergic DRD2-C32806T receptors and the enzymes dopamine β-hydroxylase DBHG1368A) could increase the efficacy of drugs for smoking cessation.[7]

In the specific case of Alzheimer's disease, several mutations and polymorphisms, including apolipoprotein E4, have been associated with increased risk for this disease. Furthermore, clinical trials have demonstrated that carriers of the ApoE E3 allele respond better to cholinesterase inhibitors than those who lack the allele. There is also evidence that treatment response to non-cholinergic drugs is affected by the ApoE gene and that response to cholinesterase inhibitors is influenced by interactions with other genes involved in drug metabolism.

Another example of how pharmacogenetics is helpful is in the treatment of hyperlipidaemia, where genetic variations at the ApoE locus has been associated with fasting and postprandial plasma lipoprotein concentrations and with cardiovascular disease. The ApoE E2 polymorphism

is associated with an increased lipid-lowering response to statin therapy, whereas E4 polymorphism is associated with a decreased response to therapy. However, testing for this genetic variation is not yet part of routine clinical care.

In the near future, pharmacogenetics will give the chance to provide patients with information about their probability of responding to treatment with a particular medication, given their genotype. Although the discipline is beginning to come of age, only a few pharmacogenetic applications are currently available in clinical settings, but many promise to enter the realm of clinical practice in the next few decades.[7]

Prescribing for geriatric patients

The Beers criteria, a useful consensus for inappropriate medication use in the elderly

The purpose of this initiative was to revise and update criteria for potentially inappropriate medication use in adults aged 65 years and older in the USA. The reviewed criteria covered two types of statements: (1) medications that should be avoided in persons older than 65 years and (2) medications that should *not* be used in persons known to have specific medical conditions.[8]

The Beers criteria identify 48 individual medications or classes of medications to avoid in older adults and their potential concerns and 20 diseases and conditions and medications to be avoided in older adults with these conditions. Adverse drug events have been linked to preventable problems in the elderly patients, such as depression, constipation, falls, immobility, confusion and hip fractures.

The 1997 study on adverse drug reactions found that 35% of ambulatory older adults experienced an adverse drug event and 29% required healthcare services; some nursing facility residents have one of these events over a 4 year period. In summary, these criteria have been extensively used for evaluating and intervening in medication use in older adults over the past decade. However, owing to the continuous arrival of new medications on the market, increased knowledge about older drugs and side effects from the new ones needs to be updated periodically in order to keep physicians updated on how to avoid undesirable medication side effects in the elderly population (Table 13.6).[8]

Clinical strategies

The quality of life for the older patient can be greatly enhanced with the intelligent use of medications and keeping certain key points in mind. A major problem when facing elderly populations is the fact of prescribing multiple and occasionally unnecessary medications with increased risk of significant drug interactions; establishing a diagnosis is critical to avoid treating a symptom with hit or miss drugs versus treating a specific condition. Discussions about geriatric pharmacology are frequently centred around age-related changes in drug pharmacokinetics and pharmacodynamics; nonetheless, non-pharmacological factors can play an even greater role in the safety and effectiveness of drug therapy in the geriatric population.

Frequently, neither the patient nor the healthcare provider has a clear picture of the total drug regimen. New patients undergoing initial geriatric assessment should be asked to empty their medicine cabinets and to bring all bottles to their first appointment. When asking the patient about their medication, it is important to be specific about prescription medications, over-the-counter products, as-needed medications, vitamins, minerals, herbal products and home remedies.

Compliance

Compliance is a major problem in all persons and particularly so in many older persons. Cognitive impairment, depression, decreased hearing and poor vision can all lead to failure to take a drug or for the drug to be taken inappropriately. Instructions on how to take drugs need to be written in large letters with legible handwriting. The healthcare professional needs to check that the patient understands the instructions. Pill boxes need to be set up for older persons having problems remembering to take their medicines.

When choosing the dose of a medication for an older patient, always remember to *start slow, go slow and do not stop too soon*. Initially, doses should be modified on the basis of pharmacokinetic predictions, but actual pharmacodynamic responses to the medication should be used to adjust the dose. If the pharmacokinetic information is not available, doses can be initiated at half the usual adult dose; this can be achieved by splitting tablets or by extending the dosing interval. Minimizing the number of doses per day is easier for the patient and can improve compliance. The use of sustained-release dosage forms or taking advantage of prolonged elimination half-lives in older persons can decrease the number of doses per day.

Cost is a key factor in compliance. Drug costs need to be noted at the time of prescribing, and patients need to be asked if they can afford the drug. It is useful to remember that cheap drugs (e.g. thiazides, β-blockers and reserpine) often perform approximately as well as more expensive drugs. Most pharmaceutical companies have programmes to help persons obtain drugs they cannot afford.

There is an increasing recognition that failure to treat an older person appropriately may be as bad as overtreating. For example, failure to use β-blockers following myocardial infarction would be a clear error of omission. However, it has been shown that atenolol (a cheap once-per-day β-blocker) performs better than the more expensive twice-per-day β-blockers. Most older persons in nursing homes have osteopenia or osteoporosis, yet they do not receive

Table 13.6 Inappropriate medication use in older adults: considering conditions and diagnoses.[a]

Condition	Drug	Comments
Heart failure	Disopyramide, high sodium content drugs (alginate, bicarbonate, phosphate)	Negative inotropic effect. Potential to promote fluid retention and exacerbation of heart failure
Hypertension	Phenylpropanolamine hydrochloride (removed in 2001), pseudoephedrine, diet pills, amphetamines	May produce elevation of blood pressure secondary to sympathomimetic activity
Gastric or duodenal ulcers	NSAIDs and aspirin >325 mg per day	May exacerbate existing ulcers or produce new ones (COX-2 excluded)
Seizures or epilepsy	Clozapine, chlorpromazine, thioridazine	May lower seizure thresholds
Blood clotting disorders or on anticoagulant therapy	Aspirin, NSAIDs, dipyridamole, ticlopidine, clopidogrel	May prolong clotting time and elevate INR values or inhibit platelet aggregation resulting in increased potential for bleeding
Bladder outflow obstruction	Anticholinergics and antihistamines, GI antispasmodics, muscle relaxants, anticholinergics, antidepressants	May decrease urinary flow, leading to urinary retention
Stress incontinence	α-Blockers, anticholinergics, tricyclic antidepressants, long-acting benzodiazepines	May produce polyuria and worsening of incontinence
Arrhythmias	Tricyclic antidepressants	Proarrhythmic effect and ability to produce QT interval syndrome
Insomnia	Decongestants, theophylline, methylphenidate, amphetamines	Concern about CNS stimulant effects
Parkinson's disease	Metoclopramide, conventional antipsychotics	Concern about anticholinergic/dopaminergic effects
Cognitive impairment	Barbiturates, anticholinergics, antispasmodic, muscle relaxants	Concern about CNS-altering-effects
Depression	Long-term benzodiazepine use, sympatholytic agents (methyldopa, reserpine)	May exacerbate depression
Anorexia and malnutrition	CNS stimulants, fluoxetine, methylphenidate	Concern about appetite-suppressing effects
Syncope/falls	Short- to intermediate-acting benzodiazepines, tricyclic antidepressants	May induce ataxia, impaired psychomotor activity
SIADH/hyponatraemia	Fluoxetine, citalopram, fluvoxamine, paroxetine, sertraline	May cause SIADH
Obesity	Olanzapine	May stimulate appetite
COPD	Long-acting benzodiazepines, propranolol	May induce respiratory depression
Chronic constipation	Tricyclic antidepressants, anticholinergics, calcium channel blockers	May exacerbate constipation

[a]NSAIDs, non-steroidal anti-inflammatory drugs; GI, gastrointestinal; CNS, central nervous system; SIADH, syndrome of inappropriate ADH secretion; COPD, chronic obstructive pulmonary disease.
Source: Fick and Cooper.[8]

calcium with vitamin D and bisphosphonates. Many older persons have anaemia and chronic renal failure; despite evidence that treatment with erythropoietin or darbepoetin alfa improves outcomes including quality of life, they are rarely prescribed. However, the other side of the coin is overtreatment of conditions; for example, there is no evidence for treating blood pressure below 160/90 mmHg in older persons and even less for primary prevention of heart disease by lowering cholesterol in octogenarians. When calcium or iron is administered with other drugs they block their absorption, leading to inadequate dosing. Commonly in older persons on multiple medications, an agonist and an antagonist of the same drug class are prescribed for different indications, for example, a cholinesterase inhibitor for Alzheimer's disease and an acetylcholine inhibitor for incontinence. The ridiculousness of this concept is self-evident and leads to multiple side effects.

There are many factors that contribute to the underuse of beneficial therapies in the geriatric patient population. Physicians may fail to prescribe potentially beneficial medications to elderly patients owing to the scarcity of data on which to base pharmacotherapeutic decisions or for fear of causing adverse drug events in patients who are already using multiple medications. While some may consider this practice to represent therapeutic nihilism, others may consider it to be prudent prescribing. A fair and balanced assessment of the issue of undertreatment of elderly patients must give consideration to three important

areas: (1) the lack of high-quality evidence derived from clinical studies with relevance to treating the older patient with multiple chronic medical conditions; (2) the need for systems of care that improve drug safety and enhance adherence in elderly persons on complex medication regimens; and (3) the persistence of financial barriers to access to medications.[2,9]

The Division of Geriatrics at Saint Louis University has developed many different resources to teach both physicians and patients in the field of geriatric medicine. The development of mnemonics, specifically a mnemonic developed towards avoiding polypharmacy, has been very successful:

Guidelines for proper medication prescribing and medication reduction

Alternatives
Vague history or symptoms
OTC (over-the-counter) medications also have side effects
Interactions (drug–drug, drug–disease)
Duration
Therapeutic versus preventive
Once per day versus twice or four times per day
Other doctors
Money
Adverse effects of other drugs
Need
Yes/no (is the person actually taking the medication?)

The use of large numbers of medications will always be a key factor of the medical–scientific care of the growing older population around the world. However, there is always a grey area where there is concern about avoiding the excessive use of drugs and providing access to therapeutic guidelines that might have beneficial effects on morbidity and mortality, function and quality of life. The health system should address this issue, focusing on including more elderly people in clinical trials, especially patients with multiple comorbidities. The implementation of efforts towards the development of interdisciplinary teams to care for elderly patients and the use of information technology to improve medication adherence and safety should be encouraged.

Key points

- Cheap drugs have been around for a long time and, as such, are more likely to have their side effects in people well known.
- Older persons take more medications than their younger counterparts.
- The older body does not accommodate drugs in the same manner as the younger body does.
- There is no such thing as an absolutely safe drug.
- Elderly patients are more likely to experience undesirable side effects from drugs than are younger persons.
- Always 'start slow and go up slow'.

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CHAPTER 14

Patient safety

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Introduction

History and evolution of the concept of patient safety

The practice of medicine, aptly described by Samuel Johnson as 'the greatest benefit to mankind', has and always will be associated with inherent risks.[1] This has been acknowledged for as long as medicine itself has existed: the Ancient Greeks' words for 'kill' and 'cure' were similar and the Hippocratic Oath contains the promise 'to abstain from doing harm', later adapted by Thomas Sydenham into the famous phrase '*primum non nocere*' or 'first do no harm'.

Perhaps surprisingly, it has only been relatively recently that these risks, their causes and ways to ameliorate them have been subjected to rigorous academic study. One of the earliest specific observations of patient harm was made in the nineteenth century by Florence Nightingale regarding infection in hospitals, a new and devastating problem at the time. In the 1960s, more systematic studies of hospital-associated harm began to be carried out, initially driven by the development of litigation. In more recent times, perhaps triggered by high-profile events such as the Bristol Heart Inquiry and landmark international reports such as *An Organization with a Memory*[2] in the UK and *To Err is Human*[3] in the USA, patient safety has become the focus of much attention. It is now recognized globally as one of the top priorities in healthcare and, as our understanding of healthcare-related harm deepens, so our ability to improve it grows.

In this chapter, we describe some of the current knowledge about patient safety and how this relates to the care of older people.

Definitions

Patient safety may be defined as 'the prevention and amelioration of adverse outcomes or injuries stemming from the process of healthcare'.[4] This definition encompasses not only the avoidance of individual error or harm and the high reliability of healthcare systems, but also the appropriate management of healthcare-associated harm: not just in terms of appropriate immediate medical management, but also in supporting staff, patients and their families.

Patient safety is just one aspect of high-quality care. In the recent UK report *High Quality Care for All*,[5] quality of care, defined from a patient's point of view, encompasses safety, experience and outcomes. In the USA, 'Crossing the quality chasm' similarly described the elements of quality as safety, effectiveness, patient-centredness, timeliness, efficiency and equitableness. Safety has been described as 'the dark side of quality' because of its historical association with litigation and blame, but it is increasingly acknowledged that efforts to learn more about and improve safety are themselves a feature of high-quality healthcare organizations.[1]

Measurement – the scale of harm

There are several ways to measure or estimate the extent of errors or adverse events in healthcare, including analysis of administrative or reporting data, case record review, observations of patient care and active clinical surveillance. Each of these methods has its advantages and disadvantages, in terms of availability of data, cost, reliability, observer bias and clinical relevance. Clearly, the measurement of safety overlaps with the measurement of quality of care, described in Chapters 137 and 138.

An adverse event is defined as an unintended injury caused by medical management rather than the disease process, which is sufficiently serious to lead to prolongation of hospitalization or to temporary or permanent disability or death.[4] This definition is important because it has been traditionally used in studies of the nature and scale of harm, described below.

A critical incident or 'near miss' may be considered to be the next step down from this – incidents which may have caused harm but did not actually do so.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 14.1 International adverse events studies, showing data for older patients.

Study	Year	No. of subjects	No. (proportion, %) of elderly subjects	Definition of elderly (years)	Overall adverse event rate (%)	Incidence in elderly (%)	Incidence in young (%)	Difference
California (Mills)	1977	20 864	3826 (18.34%)	≥65	4.65	7.22 ± 0.82	4.07 ± 0.30	$p < 0.05$
Harvard (Brennan)	1991	30 121	4980 (16.53%)	≥65	3.7	Standardized for DRG 5.7 ± 0.6	2.6 ± 0.2 (16–44 yrs)	$p < 0.0001$
Australia (Wilson)	1995	14 210	3945 (27.76%)	≥65	16.6	23.3	Mean 13.75	Not given
Utah and Colorado (Thomas)	2000	15 000	Not stated	≥65	2.9 ± 0.2	All adverse events 5.29 ± 0.37	All adverse events 2.80 ± 0.18	$p = 0.001$
UK (Vincent)	2001	1014	342 (33.73%)	≥65	10.8	18.13 (62/342)	7.25 (48/662)	$p < 0.001$
New Zealand (Davis)	2002	6579	1967 (29.9%)	≥65	11.2	17.6 (346/1967)	10.93 (504/4612)	Not given
Canada (Ross-Baker)	2004	3745	Not stated	Not stated	7.5	Mean age of patient with adverse events 64.9 (SD 16.7) vs 62.0 (SD 18.4) yrs, $p = 0.016$		
Ottawa (Forster)	2004	502	126 (25.1%)	>72	12.7	22.22 (28/126)	9.57 (36/376)	$p < 0.001$
France (Michel)	2007	8754	Not stated	Not stated	6.6 per 1000 days of hospitalization	Mean age of those experiencing adverse events = 63 yrs, 61.7 yrs for those who did not ($p = 0.5$)		
UK (Sari)	2007	1006	332 (33.0%)	≥75	8.7	13.5 (95% CI 9.8–17.2)	6.2 (95% CI 4.4–8.0)	$p < 0.001$

Over the last 40 years, a number of international adverse event studies have been published, in which retrospective case record review was used to identify adverse events in order to assess the nature and scale of harm in acute hospitals.

A selection of these studies are shown in Table 14.1. Rates of adverse events in most recent studies lie between 8 and 12%, a range now accepted as being typical of advanced healthcare systems. The rate per patient is always slightly higher, as some patients suffer more than one event and about half of adverse events are generally judged to be preventable. United States rates are much lower, Australian seemingly much higher. The lower US rates might reflect better quality care, but most probably reflect the narrower focus on negligent injury rather than the broader quality improvement focus of most other studies.

Studies of errors

There are a number of methods of studying errors and adverse events, each of which has evolved over time and been adapted to different contexts.[6] Each of the methods has particular advantages and disadvantages. Some methods are oriented towards detecting incidence of errors and adverse events (Table 14.2), whereas others address their causes and contributory factors (Table 14.3). There is no perfect way of estimating the incidence of adverse events or of errors. For various reasons, all of them give a partial picture. Any retrospective review is vulnerable to hindsight or outcome, bias, where knowledge that the outcome was bad leads to unjust simplification and criticism of preceding events. Record review is comprehensive and systematic, but by definition is restricted to matters noted in the medical record. Reporting systems are strongly dependent on the willingness of staff to report and are a very imperfect reflection of the underlying rate of errors or adverse events.

Why do adverse events occur?

In order to obtain a true understanding of patient safety, it is not enough just to assess the scale of healthcare-associated harm: we have to look deeper to understand the processes that underlie it. As described later, attempts to understand the causes of adverse events are routinely made within individual organizations in several ways, such as through local morbidity and mortality meetings or through the use of more structured approaches such as root cause analysis.

Learning from other industries

On a more general level, many methods have been employed by patient safety researchers to enhance our knowledge of the causes of adverse events. It is important to appreciate that when an adverse event occurs we may be quick to judge or blame the actions or omissions of individuals, but careful inquiry usually shows us that deficiencies in our systems are also at fault. We have learnt much from other industries in this respect. Investigation of major disasters such as the Chernobyl nuclear explosion, the Space Shuttle Challenger crash and the Paddington rail

Table 14.2 Methods of measuring errors and adverse events.

Study method	Advantages	Disadvantages
Administrative data analysis	Uses readily available data	May rely upon incomplete and inaccurate data
	Inexpensive	The data are divorced from clinical context
Record review/chart review	Uses readily available data	Judgements about adverse events not reliable
	Commonly used	Medical records are incomplete
		Hindsight bias
Review of electronic medical record	Inexpensive after initial investment	Susceptible to programming and/or data entry errors
	Monitors in real time	Expensive to implement
	Integrates multiple data sources	
Observation of patient care	Potentially accurate and precise	Time consuming and expensive
	Provides data otherwise unavailable	Difficult to train reliable observers
	Detects more active errors than other methods	Potential concerns about confidentiality
		Possible to be overwhelmed with information
Active clinical surveillance	Potentially accurate and precise for adverse events	Time consuming and expensive

Source: adapted from Thomas and Petersen.[6]

Table 14.3 Methods of understanding errors and adverse events.

Study method	Advantages	Disadvantages
Morbidity and mortality conferences and autopsy	Can suggest contributory factors	Hindsight bias
	Familiar to healthcare providers	Reporting bias
		Focused on diagnostic errors
		Infrequently used
Case analysis/root cause analysis	Can suggest contributory structured systems approach	Hindsight bias
	Includes recent data from interviews	Tends to focus on severe events
		Insufficiently standardized in practice
Claims analysis	Provides multiple perspectives (patients, providers, lawyers)	Hindsight bias
		Reporting bias
		Non-standardized source of data
Error reporting systems	Provide multiple perspectives over time	Reporting bias
	Can be a part of routine operations	Hindsight bias

Source: adapted from Thomas and Petersen.[6]

accident identified 'violations of procedure' or problems that occurred as the result of actions or omissions by people at the scene. However, further analysis of these events revealed 'latent conditions'[7] further upstream in the process, which allowed these violations to occur and have such a devastating effect. 'Latent conditions' are often a result of gradual and unintentional erosion of safety-enhancing processes because of other pressures, for example, cutting training budgets because of financial costs. Further still in the background are often deeply ingrained cultural and organizational issues, some of which may be elusive and difficult to resolve.

Of course, it is all very well to learn about the underlying causes of these non-healthcare-related disasters, but the question that most clinicians will ask at this stage is what relevance this has to us. Although healthcare is similar to these industries in some respects, such as the high level of inherent risks and the well-meaning and dedication

Table 14.4 Examples of some cognitive biases and heuristics that commonly affect clinical reasoning.

Name	Definition	Example
Availability heuristic	Making judgements based on cases that spring easily to mind	'The last time I saw a patient with fever and a headache it was only flu, so it is likely to be so in this case too' (actually meningitis)
Anchoring heuristic	Sticking with initial impressions	The confused elderly patient who has a 'UTI' on admission (despite a negative MSU), whose severe constipation goes unnoticed
Framing effects	Making a decision based on how the information is presented to you	'A&E referred this patient with fever and haemoptysis as ''pneumonia'' so that is the most likely diagnosis even though the CXR is normal' (actually a PE)
Blind obedience	Showing undue deference to seniority or technology – 'they must be right and I must be wrong'!	'My consultant said that this patient could go home, so I am going to ignore concerns raised by nursing staff' 'The blood results show a normal haemoglobin even though this patient looks clinically anaemic – the blood results must be right'
Premature closure	Being satisfied too easily with an explanation	In a patient with staphylococcal sepsis, assuming the source of sepsis is their cellulitic leg, and missing their underlying endocarditis

Source: adapted from Redelmeier.[10]

of its staff, it is very different in others – such as in its diversity, often non-centralized administration, uncertainty and unpredictability.

Human error

Human error is not easy to define, as boundaries are often blurred between the actions or inactions of individuals and the deficiencies of the systems in which they work. However, it is important to try to define and classify different sorts of error in medicine, largely because this may help us to learn from incidents. We can think about errors in medicine in relation to the clinical processes involved, for example, prescribing errors or diagnostic errors, but perhaps it is also useful to look at the underlying psychological themes. In his analysis of different types of error, Reason[8] divided them into two broad types of error: slips and lapses, which are errors of action and mistakes which are, broadly speaking, errors of knowledge or planning. He also discusses violations that, as distinct from error, are intentional acts which, for one reason or another, deviate from the usual or expected course of action.

Delays and errors in clinical decision-making are particularly critical in medicine and there is an extensive literature about the complexities of medical decision-making.[9] In our daily clinical practice, we use heuristics, which are simple but approximate rules to aid decision-making by simplifying the situation and decision to be made. Particularly at times of fatigue, stress or time pressure, these heuristics can become 'biases', leading to faulty clinical decision-making leading to undesirable consequences.[10] Some of these, with common clinical examples, are given in Table 14.4.

System and organizational factors

Errors and human behaviour cannot be understood in isolation, but only in relation to the context in which people are working. Clinical staff are influenced by the nature of the task they are carrying out, the team they work in, their working environment and the wider organizational context; these are the system factors. The systems in which we work have inbuilt defences and barriers and it is only when these defences are simultaneously breached that adverse events occur. This concept forms the basis of Reason's 'Swiss cheese model', shown in Figure 14.1.

Learning from high-reliability organizations in other industries, which achieve high levels of safety and performance in the face of considerable hazards and operational complexity, is an ongoing challenge to improving safety in healthcare. Important characteristic of these types of organizations are safety culture and leadership: there is

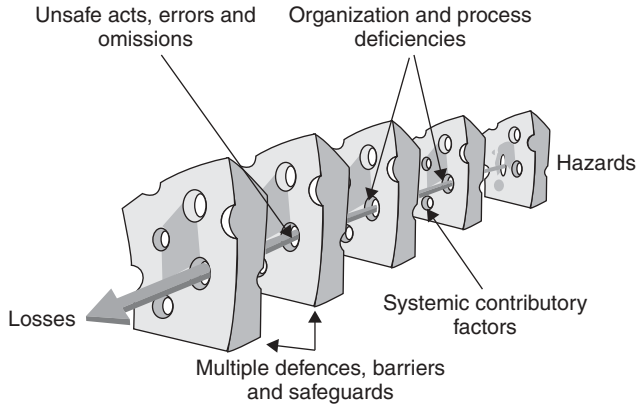


Figure 14.1 Reason's Swiss cheese model.

some evidence that these are related to some measures of safety in healthcare.

Analyses of incidents usually reveal the causes to be a combination of all of the factors described above. This can be summarized by 'the seven-level framework',[11] which conceptualizes the patient, task and technology, staff, team, working environment and organizational and institutional environmental factors that influence clinical practice. This is shown in Table 14.5.

What happens after an adverse event?

Reporting and learning

There are a variety of reporting systems operating at different levels within healthcare systems across the world. Some operate primarily at local level (risk management systems in hospitals), others at regional or national level. Local systems are ideally used as part of an overall safety and quality improvement strategy, but in practice may be dominated by managing claims and complaints. Many different clinical specialities, particularly anaesthesia, have established reporting systems to assist them in improving clinical practice. These systems are designed to provide information on specific clinical issues which can be shared within the professional group. The increasing attention paid to patient safety has led to the establishment of many new reporting and learning systems, most notably, in the UK, the Reporting and Learning System (RLS) established by the National Patient Safety Agency. Other national reporting systems include the wide-ranging Veterans Affairs system in the USA and the Australian Incident Monitoring System (AIMS).

The main purpose of reporting systems is to communicate information about patient safety issues, so that learning and improvement of systems and practice can occur. A secondary benefit of these systems is that we can use them to assess the scale of harm and identify trends.

Table 14.5 The seven-level framework.

Factor types	Contributory influencing factor
Patient factors	Condition (complexity and seriousness)
	Language and communication
	Personality and social factors
Task and technology factors	Task design and clarity of structure
	Availability and use of protocols
	Availability and accuracy of test results
	Decision-making aids
Individual (staff) factors	Knowledge and skills
	Competence
	Physical and mental health
Team factors	Verbal communication
	Written communication
	Supervision and seeking help
	Team leadership
Work environmental factors	Staffing levels and skills mix
	Workload and shift patterns
	Design, availability and maintenance of equipment
	Administrative and managerial support
	Physical environment
Organizational and management factors	Financial resources and constraints
	Organizational structure
	Policy, standards and goals
	Safety culture and priorities
Institutional context factors	Economic and regulatory context
	National health service executive
	Links with external organisations

Source: from Vincent *et al.*[11]

There are inherent problems with all reporting systems in healthcare: most studies have found that reporting systems only detect 7–15% of adverse events,[12] when compared with other methods of detection such as case record review. Some of the common barriers to reporting include a fear of embarrassment, punishment by oneself or others, fear of litigation, lack of feedback and a belief that nothing will be done in response to reporting.

Understanding why things go wrong

The investigation and analysis of cases in which clinical incidents have occurred can be used to illustrate the process of clinical decision-making, the weighing of treatment options and sometimes, particularly when errors are discussed, the personal impact of incidents and mishaps, and critically also includes reflection on the broader healthcare system. There are a number of methods of investigation and analysis used in healthcare, either retrospectively, for example root cause analysis or systems analysis of events, or prospectively, for example failure modes and effects analysis (FMEA).

Caring for patients after an adverse event

Patients and relatives may suffer in two distinct ways from a medical-induced injury: first from the injury itself and second from the way in which the incident is handled afterwards. Many people harmed by their treatment suffer further trauma through the incident being insensitively and incompetently handled. Conversely, when staff come forward, acknowledge the damage and take positive action, the support offered can ameliorate the impact in both the short and long term. Injured patients and their families need open disclosure: an explanation, an apology, or to know that changes have been made to prevent future incidents, and often also need practical and financial help.[13]

Supporting staff

Making an error, particularly if a patient is harmed because of it, may have profound emotional or psychological consequences for the staff involved. This in turn can make future errors more likely and affect teamwork. Factors which may make this more likely include the severity of the error and the reactions of those involved, attitudes to error, beliefs about control and the power of medicine and the impact of litigation. Strategies to minimize the effects of adverse events on staff include wider acknowledgement of the potential for error, having an agreed policy on openness with injured patients, encouraging support from colleagues, education and training and, if necessary, formal support and access to confidential counselling.

Patient safety and older people

The incidence of adverse events in older people in hospital

Re-analysis of the international adverse event studies

There is considerable evidence that older people suffer a higher incidence of adverse events than their younger counterparts in hospital. The landmark, international, adverse event studies described in Table 14.1 investigated the incidence and types of adverse events in hospital inpatients of all ages. This was achieved by two-stage retrospective case record review in the majority of cases. Table 14.1 also shows that if the results of these large studies are re-analysed to consider specifically the effects of age on patterns and frequencies of adverse events, they all show that age is a risk factor for adverse events. However, when this relationship is examined more closely, it emerges that it is co-morbidity, rather than age alone, that appears to be responsible for this association. In addition to experiencing more adverse events, older people also suffer more serious consequences of adverse events in the majority of studies, in terms of morbidity and mortality, increased dependence, increased hospital stay and a greater chance of institutionalization;[14] again, this seems to be related to their physical vulnerability, in terms of frailty and diminished physiological reserve. As might be expected, data from these studies show that older people in hospital tend to experience different types of adverse events than their younger counterparts, such as falls, hospital-acquired infections and drug errors rather than complications related to invasive procedures. In general, it seems that it is controversial as to whether adverse events are more preventable in elderly than in younger patients.

Data from reporting systems

Another way of estimating the incidence of hospital-related harm in older people is to analyse data from local and national reporting systems. The incidents most commonly reported to the NRLS in acute hospitals are patient-related accidents, which in older people are most likely to be falls. These are followed closely by problems related to medication. Data sources such as this are very useful in terms of allowing us to prioritize areas for intervention. However, it is important to bear in mind that many problems go unreported, particularly those which may not be as obvious as falls or drug errors, so the scale and nature of adverse events may not be truly reflected in this way.

Types of adverse events experienced by older people in hospital

The geriatric syndromes

During the hospital stay itself, older people are of course vulnerable to the same adverse events as their younger counterparts, such as hospital-acquired infection, adverse drug events, deep vein thrombosis and procedure-related complications. As described above, there is evidence that the incidence of these types of adverse events is greater in older patients and their consequences are more severe. However, the process and effects of hospitalization in older people, particularly those who are frail with multiple comorbidities, are different to those in younger people; it therefore follows that any analysis of patient safety and adverse events in this vulnerable population should be undertaken in this context. Figure 14.2 illustrates this, in a proposed scheme for the effects of hospitalization in frail older people.

Older people may be admitted to hospital because of an acute illness, acute exacerbation of a chronic disease process, side effects of treatment for these conditions or the development of a new 'geriatric syndrome'. These are similar to the 'geriatric giants' first coined by Isaacs in 1965 (immobility and instability, incontinence and impaired intellect) and are now understood to include delirium, falls, incontinence, pressure sores, depression, undernutrition, constipation and functional decline. Older patients very commonly have one or more of these conditions at the time

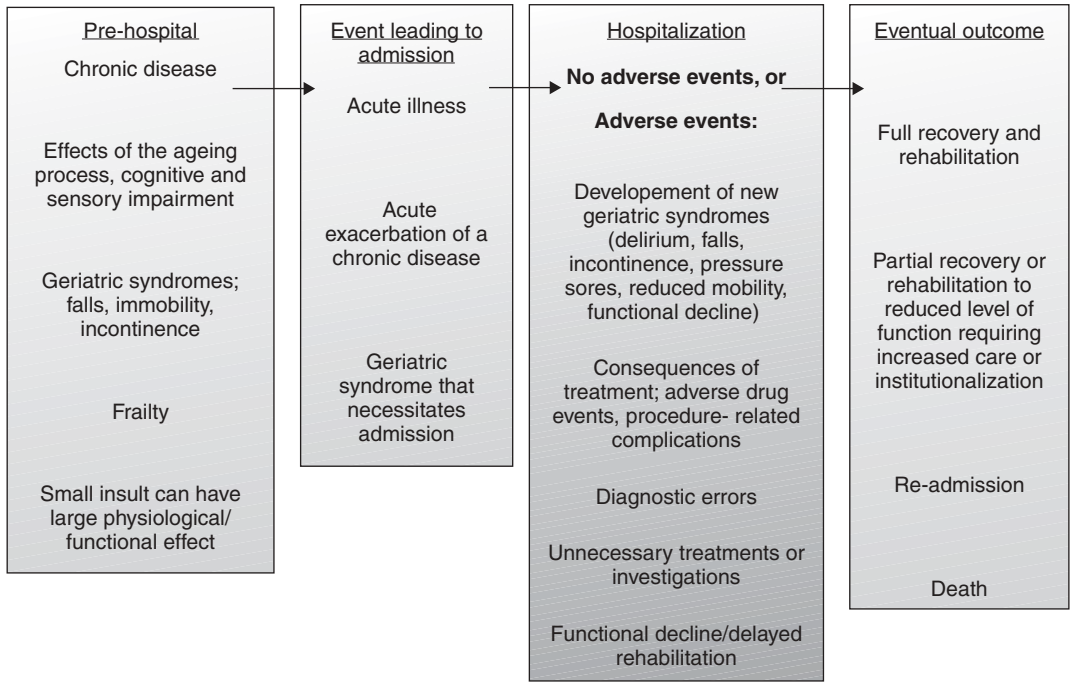


Figure 14.2 A proposed scheme for the effects of hospitalization in frail older people.

they are admitted to hospital, but there is a strong argument that if any of these truly occur *de novo* during the inpatient stay and are not related solely to progression of disease, each should be considered to be an adverse event because of their association with increased mortality and morbidity and the strong evidence that they are largely preventable.[15]

The geriatric syndromes rarely occur in isolation – during the complex, lengthy hospital admissions often experienced by older people, they are often interlinked and may contribute to downward spirals in progress and outcome. They can each contribute or be outcomes of each other; this is illustrated in Figure 14.3, which shows three common

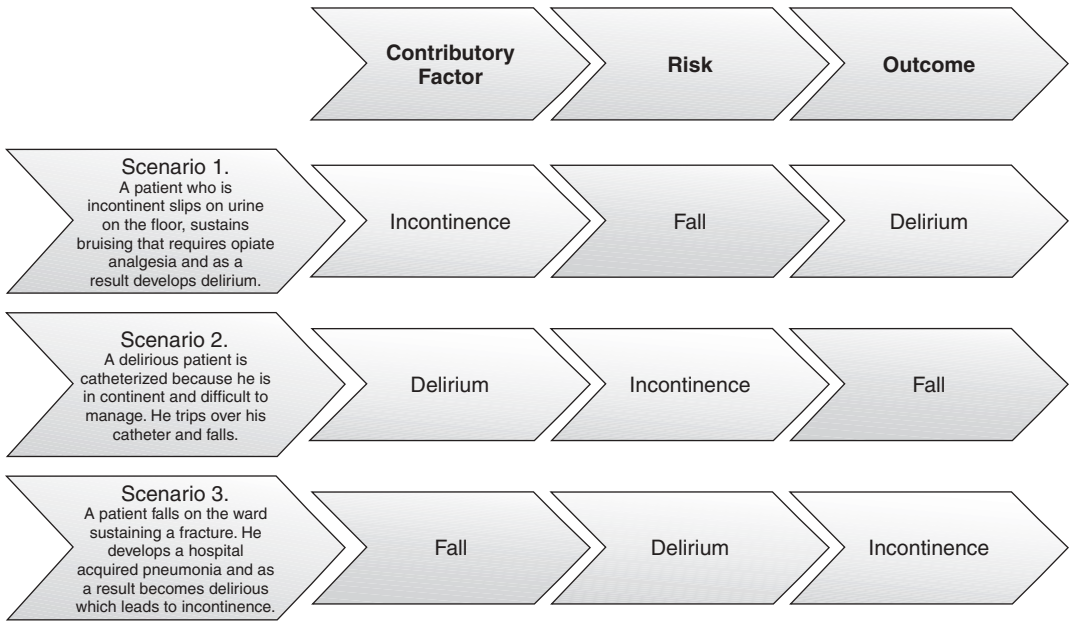


Figure 14.3 Three common clinical scenarios where delirium, incontinence and falls occur in different sequences.

Box 14.1 Adverse events in older people.

The geriatric syndromes, which could be considered to be preventable adverse events if they arise *de novo* in older people in hospital and are not related solely to progression of disease:

- Functional decline
- Loss of mobility
- Urinary or faecal incontinence
- Delirium
- Severe constipation
- Pressure sores
- Falls
- Malnutrition and/or dehydration
- Depression

Other common adverse events in older people:

- Hospital acquired infection (in older patients notably aspiration pneumonia and catheter-associated infections)
- Adverse drug events
- Venous thromboembolism
- Procedure-related complications

clinical scenarios where delirium, incontinence and falls occur in different sequences.

A summary of common adverse events in older people is shown in Box 14.1.

Preventable functional decline as an adverse event

Functional decline, defined as a decrement in physical and/or cognitive functioning which leads to a reduced ability to perform the 'activities of daily living' (ADLs) that are necessary to live independently is a common outcome for older people in hospital, regardless of whether or not any adverse events or geriatric syndromes occur during their stay in hospital. The dangers of believing the misconception that bed rest is good for hospitalized patients was succinctly put by Asher in 1947:[16]

> It is always assumed that the first thing in any illness is to put the patient to bed. Hospital accommodation is always numbered in beds. Illness is measured by the length of time in bed. Doctors are assessed by their bedside manner. Bed is not ordered like a pill or a purge, but is assumed as the basis of all treatment. Yet we should think twice before ordering our patients to bed and realize that beneath the comfort of the blankets there lurks a host of formidable dangers. . . . Teach us to live that we may dread unnecessary time in bed. Get people up and we may save our patients from an early grave.

Unfortunately, older patients are still often confined to bed more than is necessary and functional decline remains an extremely common problem in more modern times; in one study, one-third of elderly patients had lost at least one ADL by the time they left hospital.[17]

Functional decline that occurs during hospitalization can impact on the older person (and the healthcare system) in several ways: it can lead to loss of independence necessitating increased care requirements (and even institutionalization), depression and reduced quality of life. Like the other 'geriatric syndromes', many cases of functional decline are avoidable during a hospital admission if proper measures are taken to prevent it. Once consequence of the diminished reserves associated with frailty and age is that when functional decline occurs, it may be irreversible or require a prolonged period of rehabilitation to achieve partial or complete reversal. When functional decline occurs, the often prolonged hospital stays required for rehabilitation after serious illness, although often unavoidable, bring further risks.

Adverse drug events in older people

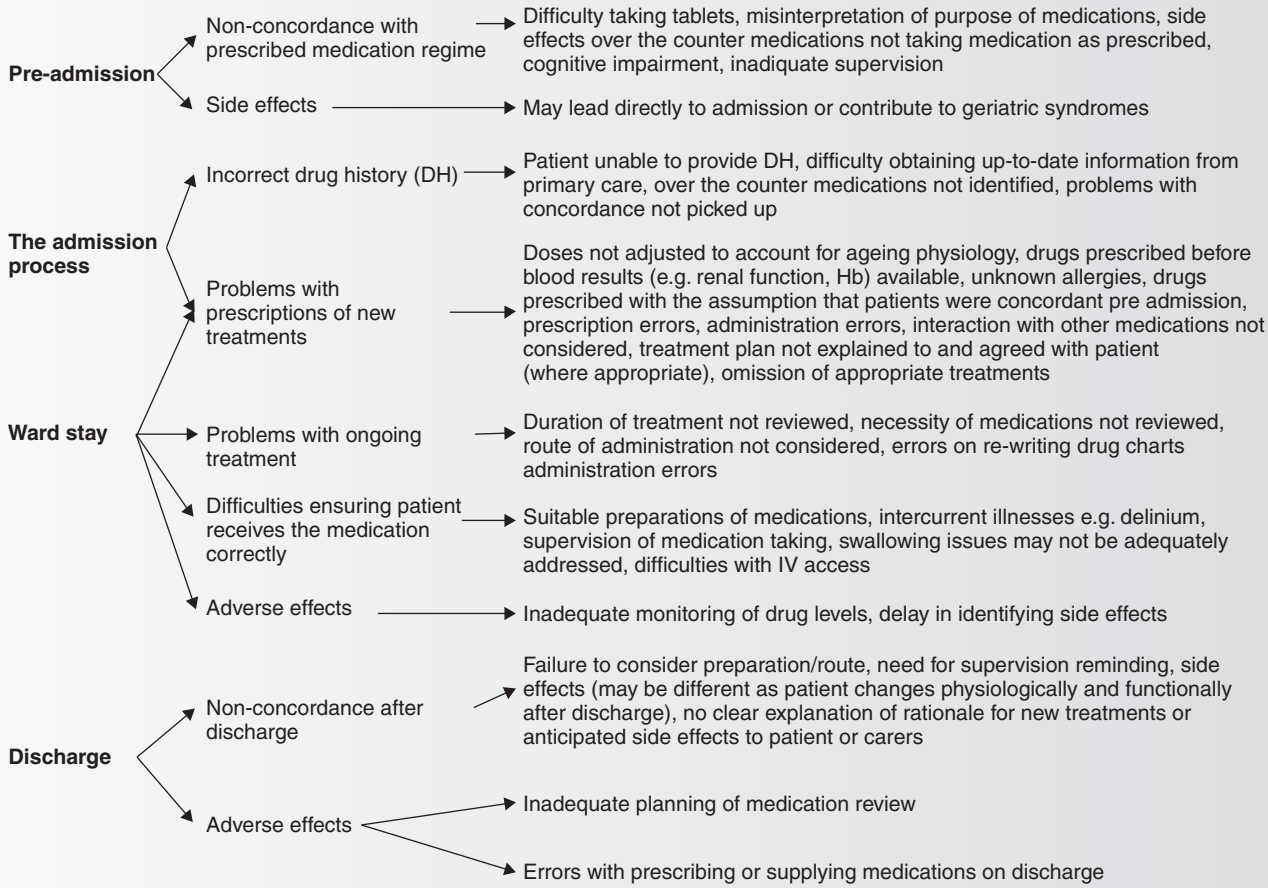
The term 'adverse drug event' covers a wide range of medication-related problems, encompassing the following: errors in prescription, preparation or administration, adverse drug reactions (which may be further subclassified into Type A, predictable, or Type B, bizarre)[18] or problems with concordance. These may occur as a result of appropriate or 'inappropriate' (under-, over- or mis-) prescribing.

As with other adverse events in hospital, at first glance the incidence of adverse drug events seems to increase with age, but there is some evidence that they are actually directly related to complexity and comorbidity rather than age alone. Recent studies have estimated the incidence of adverse drug events in older people in hospital to be between 31.9 and 37%.[19] As with all estimates of hospital-associated risks, this figure depends very much on the definitions and methodologies used. Nevertheless, even when relatively strict definitions are used, adverse drug events are the most common adverse events to affect hospitalized patients of all ages.[20]

The over-60s are the highest users of medications, receiving 59% of dispensed prescriptions in the UK.[21] Polypharmacy is an important issue – one-fifth of people aged over 70 years take five or more medications.[22] Virtually all older patients who are admitted to hospital are given drug treatment of some description. It would be unusual for an older patient not to have been taking any medications prior to admission or for these not to have changed in some way by the time of discharge.

Adverse drug events are also a significant cause of admission to hospital in older people (estimated at 6.5% of admissions, with a median length of stay of 8 days[23]). Furthermore, patients who were admitted because of an adverse

Box 14.2 Common types of medication-related problems in older people in hospital.



drug event go on to have a significant chance (17.7%[24]) of subsequent readmission due to further adverse drug events. Box 14.2 shows the common types of medication-related problems that may occur at different stages of the hospital admission process in an older person.

Outside hospital, the highest users of medications are care home residents. A recent study in the UK showed that the incidence of medication errors in nursing home residents was as high as 69.5%.[25] The categories of error found were similar to those in Box 14.2 – they included prescribing, monitoring, dispensing and administration errors. The underlying causes of the errors both in hospital and in care homes relate to common underlying patient safety themes: system failures, individual errors, communication problems within and between healthcare teams and with the patient and assessment or diagnostic skills and procedures not tailored to the individual.

Certain categories of drugs are more problematic than others for older people, notably anticoagulants, opiates and other centrally acting medications. Several efforts have been made to try to identify groups of medications which pose particular risk, so that they can be more easily avoided in this population, such as those categories of drugs included in the Beers criteria.[26] The fact that common treatments such as oxygen and intravenous fluids should be treated in the same way as other drugs is sometimes forgotten; but these are potentially dangerous treatments (particularly for older patients) and should be treated with due caution. The physiological changes associated with normal ageing and the pathological changes associated with the disease processes which are common among older people in hospital all impact on the risks associated with giving medications to this population. These changes have effects on the pharmacokinetics and pharmacodynamics of virtually all medications.

Frail elderly people are rarely included in large pharmaceutical trials, which in turn may result in harm because findings from clinical trials involving younger patients may be incorrectly extrapolated to older patients. The changes that occur with age also have practical implications, in terms of drug regimens, administration and concordance; for example, swallowing difficulties,

arthritis or cognitive or visual impairment need to be taken into consideration when prescribing and administering drugs to these complex patients.

As with all patient safety issues in older people, adverse drug events do not occur in isolation – they are closely linked to the geriatric syndromes in both cause and effect. The unique characteristics of the frail elderly again play a part here – because of the often non-specific ways in which adverse drug events present in these patients (often in the form of the geriatric syndromes described above, particularly delirium or falls), they often go unrecognized and, rather than stopping causative agents, more medications are added, causing further adverse effects. This can lead to a vicious circle, which is known as the 'prescribing cascade'.[27]

Implications

The undoubtedly higher rate of adverse events in older people has obvious implications financially and for service provision. We must also consider the inescapable implications of the ageing population. By 2025, the number of people in the UK aged over 85 years will have increased by two-thirds; people aged over 65 years account for 60% of acute hospital admissions and 70% of bed days in NHS hospitals. Ensuring patient safety and high-quality care for the growing number of older patients in healthcare systems might be seen as a battle against the inevitable consequences of illness and age, combined with the negative outcomes of preventable geriatric syndromes and adverse effects of treatments and interventions.

Why are older people more susceptible to healthcare-associated harm than younger patients?

The causes of harm to patients are complex and may lie in individual error, process factors, organizational or cultural issues or wider system problems. In this section, we address a number of issues which are particularly critical in the care of older people.

The effects of comorbidity and frailty

As major international studies have shown, adverse events are not associated with age alone, but rather with comorbidity, complexity and frailty. Comorbidity is commonplace among the elderly: 98% of people over the age of 65 years in one primary care population had multiple chronic medical conditions.[28] For patients this leads to complex care needs, interacting medical conditions and polypharmacy – all of which make them more vulnerable to poorer outcomes in general, such as increased mortality and length of hospital stay. In this group, acute illness is usually associated with exacerbations of multiple coexisting chronic diseases, which interplay to produce complex physiological, cognitive and functional consequences. Of course, there is a great deal of inter-individual heterogeneity in the way in which these complexities manifest themselves. It follows that acute illness leading to hospitalization in such individuals is rarely as straightforward as it might be in a younger, fitter patient, hence more healthcare-associated harm can occur.

Frailty can be, but is not always, associated with the latter stages of chronic illnesses. Definitions vary, but frailty is understood to be a clinical syndrome in its own right, which is associated with loss of reserve in multiple organs, associated with a clinical phenotype of generalized weakness, weight loss, exhaustion and immobility.[29] This loss of reserve leads to the frail individual being less able to withstand illness and hospitalization than those without the condition.

The interaction between older people with multiple comorbidities, complexity and frailty with the healthcare system is often complicated by the fact that illness presents in different, often more non-specific ways in this population and may manifest as one of the 'geriatric syndromes' described above.

In addition, cognitive impairment and sensory impairment may make it difficult for these patients to communicate with healthcare staff, which means that they are less able to be involved in their own care than younger people, thus increasing their vulnerability to errors.

Decision-making in the care of older people

Safe and high quality of care for older people requires staff to make complex decisions about medical and non-medical matters, with the involvement of the whole multidisciplinary team and with the aim of meeting patients' best interests. This applies across the entire healthcare system, from decisions relating to the prevention and management of long-term conditions in primary care, deciding when and whether to refer or admit patients to secondary care, to making decisions relating to inpatient care and the complex planning required to maximize their safety on discharge from hospital. The challenge is to make these decisions in the safest possible way, by anticipating and pre-empting potential errors or harm and whilst always acting in the patients best interests.

Very old people, particularly those who are frail and complex, have in the past often been excluded from large clinical and pharmaceutical trials,[30] which have formed the basis of our pharmaceutical approach to treating many common conditions. To a certain extent, this is understandable: the different physiological characteristics, coexisting medical conditions and therapies associated with old age can lead to a variety of responses to drug therapy, both beneficial and adverse; these responses can be difficult to predict,

detect and adjust for accurately in terms of measured outcomes. The consequence of this is that optimal therapeutic decision-making for the individual, for instance in terms of drug dosing or combinations, may be difficult to achieve because of the lack of an appropriate evidence base. Hence a degree of clinical judgement based on the risks and benefits of treatment in the context of elderly, frail physiology needs to be used to make such decisions. Over recent years, it has become more apparent that older people are the target group for many treatments and increasingly trials have been designed with these patients in mind.[31]

Commonly used therapeutic guidelines can also be difficult to generalize to older people, and, particularly when used by those who are not *au fait* with geriatric medicine (such as relatively inexperienced prescribers or prescribers in settings which are more used to dealing with younger or fitter people), this can result in inappropriate treatments being given to frail older people, with adverse consequences which may include over- or under-treatment, for example with opiate analgesia. Even in conditions where strong consensus and clear guidelines for management exist, there is evidence that treatment remains inadequate. This is particularly true of conditions such as delirium, where appropriate management comprises a concerted team effort and a multifaceted approach. There is evidence that such guidelines are not always followed: this demonstrates the fact that if they are to be implemented universally and successfully, concomitant educational and organizational change are needed.[32]

As the needs of each individual within this population are so heterogeneous, care must be taken to tailor decision-making to the individual. Training to develop these difficult decision-making skills is also often lacking and is usually expected to develop with experience. Cognitive biases and failed heuristics[9] are more likely to occur when the information presented to the decision-maker is as complex and of varying quality as is often the case in the care of these patients. Another problem is that whereas younger people might expect and be able to take part in the clinical decision-making process, older people often prefer not to be involved to the same extent[33] or are not able to do so. When making complex decisions such as care planning near the end of life, multiple factors need to be taken into consideration, such as the health status of the patient, their values and individual goals, so that the best interests of the individual are met. All of these factors make decision-making in the frail elderly difficult and any failure in this process can lead to undesirable consequences.

Multidisciplinary team working and communication

The complex needs of elderly patients often require equally complex treatments or interventions, usually involving the combined efforts of a highly skilled multidisciplinary team. Of course, this is in general a highly beneficial way of working because decisions and clinical management are enhanced by the expertise contributed by a variety of professionals; however, teamworking can be associated with its own problems.

If optimal patient outcomes are to occur, the multidisciplinary team needs to communicate effectively. Some of the barriers to effective communication in healthcare teams described in the literature include conflict or ambiguity about individual roles within the team, perceived hierarchical difficulties and interpersonal conflict.[34] There is some evidence that this is compounded by the fact that different professions differ in their ratings of collaboration, perceived barriers to teamwork and beliefs of what the best outcomes for patients might be.[35] In addition, there can be difficulty in ensuring that team members do not work in 'silos' and have a common understanding of goals of care. If multidisciplinary teamwork is ineffective, this can adversely effect communication with patients and carers, in turn causing decisions to be made without adequately involving patients.

Of course, the wider team caring for an older person usually extends across health and social care sectors; here, coordination and continuity of care can be a problem. In particular, poor communication at times of transition of care can cause problems. It has been shown that inadequate communication at discharge from hospital, particularly in relation to medication management and monitoring arrangements, can lead to preventable readmissions in older people.[36] It is also crucial that decisions that have been made with patients about preferred levels of future intervention are adequately communicated at the time of discharge, otherwise they may be subjected to unwanted or unnecessary intervention after discharge.

Attitudes and ageism

Unfortunately, despite standard one of the UK's National Service Framework for Older People in 2001 being 'rooting out age discrimination', there is still evidence that negative attitudes towards older people, including ageism, can result in poor quality of care and problems with patient safety.[37] Ageism describes the act of discrimination against people on the grounds of age alone. Commonly cited consequences of this are that older people may be denied treatment or investigations which may be of benefit to them or that they may be subject to mislabelling or misdiagnosis.[38] For example, there are several studies showing that older people with ischaemic heart disease are less thoroughly investigated and receive less interventional treatment than younger patients, even when it is clinically indicated.[39] This is despite growing evidence that older people are likely to experience substantial benefit in terms of quality and length

of life from appropriate cardiac interventions. This may not occur as a result of overt ageism, but rather may be related to uncertainty about the best and safest clinical practice in this age group, particularly in those who are not specialists in caring for older patients. Of course, one of the unique skills of geriatricians is to be able to strike the correct balance for the individual patient between therapeutic nihilism (the avoidance of treatment entirely) and therapeutic heroism (where all interventions and treatments are given, even when there is unlikely to be any therapeutic benefit).

The care of older people in general can be regarded by some within the healthcare profession as a speciality with very little reward (in terms of clinical outcomes or prestige) for sometimes very 'heavy' physical work. This can lead to staff feeling undervalued and lacking in motivation to implement change. There can also be a negative attitude towards the patients themselves, leading to reduced dignity, loss of patient empowerment and a sense of infantilization. One of the observable manifestations of this is 'elderspeak', where patients, particularly those with cognitive or sensory impairment, are talked down to as if they are children; this lack of meaningful interaction can contribute to depression and cognitive and functional decline.

Systems and processes of care for frail older people

Frailty and comorbidity bring many challenges for healthcare systems, the greatest of which is to ensure integrated care, with seamless communication and transition between services, allowing congruent treatment plans and optimal outcomes. Transitions of care, particularly the interface between primary and secondary care in acute hospitalization (both at admission and discharge), can be particularly problematic.

The goal of care in hospital for a frail person is not just to treat their acute illness, but also to promote maximum functional recovery and independence – in other words, to prevent functional decline. This requires systems in hospital to be set up so that those patients who are frail and at risk of functional decline can be recognized and treated early to prevent adverse outcomes. However, this does not always occur, particularly when older people are admitted (justly) to areas or departments where systems are geared more towards the care of younger, fitter people (such as surgery).

There are several other systems factors that may contribute to adverse events in the care of older people in hospital. These can give rise to poor communication, for example, inadequate procedures for handover for medical and nursing staff, either between themselves when shifts change or between disciplines when decisions are made. Systems factors may also limit good communication – for example, time constraints and pressures of volume of work may not allow healthcare professionals to take the time required to assess an older person thoroughly, decide upon a good management plan, initiate it and communicate all of this effectively to the patient, their relatives and other staff caring for them. This means that even if an individual has good communication and clinical reasoning skills, the system does not always allow these to be realized to their maximum potential in optimizing patient care.

Improving patient safety for older people

Improving the safety of a clinical system requires action at many different levels, combining a focus on generic issues with attention to specific clinical problems. In this section, we first briefly address three issues that are relevant to all healthcare sectors, but particularly critical in the care of older people. These are the education and training of practitioners, improving systems of care and the potential of design and technology to enhance safety. We then consider how specific clinical issues can be tackled, addressing interventions for geriatric syndromes, hospital-acquired infections and medication safety.

Education and skills for individual practitioners

Healthcare professionals caring for older people need to be trained in the clinical reasoning and communication skills necessary to ensure safe and high-quality care in this challenging group of patients. These skills are essential for accurate and thorough initial assessment and, if lacking, may lead to diagnostic errors and subsequent mismanagement, in addition to poor overall quality. Explicit training to develop these difficult skills can be lacking and is often expected to develop with experience. Box 14.3 gives some of the individual skills or behaviours that geriatricians use to maximize patient safety in older people.

The same communication and clinical reasoning skills required for geriatric assessment are also required to detect and manage adverse events in older people once they have occurred during the hospital admission. Successful care of older people requires staff to make complex decisions about medical and non-medical matters, with the involvement of the whole multidisciplinary team and with the aim of meeting patients' best interests. In hospital, this applies to decisions regarding both the inpatient care that elderly patients receive and also the complex planning that is often required to maximize their safety on discharge from hospital. Several educational strategies have been suggested to improve clinical reasoning,[9] such as the introduction of formal critical thinking training, teaching with the use of clinical examples of cognitive biases, encouraging consideration of diagnostic alternatives, developing mental rehearsal for practical skills using simulation

Box 14.3 Some of the individual skills and behaviours that geriatricians use to maximize patient safety in older people.

1. Early detection and prevention where possible of frailty and geriatric syndromes
2. Medication review and reconciliation at every opportunity
3. Ensuring a full collateral history is taken at every available opportunity
4. Maximizing communication at times of transition of care
5. Involving patients in their care as much as possible
6. Working with management to try to improve organisational culture towards older people
7. Ensuring that basic compassionate care is carried out
8. Supporting effective MDT working, sharing goals and information as much as possible
9. Inspiring interest in the care of older people amongst juniors and other colleagues
10. Being aware of cognitive biases in decision making and the use of strategies to overcome these

or using cognitive aids such as guidelines, algorithms or hand-held computer devices.

Medical and nursing curricula should teach the recognition of frail and complex patients, so that interventions for frailty and to prevent the occurrence of the geriatric syndromes can be implemented early. Undergraduate medical education should be designed to allow future practitioners to understand the physiological differences associated with age, informing safe prescribing for older people. Increasing attention is being paid to the teaching of communication skills – these need to be designed with the specific skills required of all healthcare professionals to communicate effectively with older people, such as those with cognitive or sensory impairment.

Keeping patients safe, particularly those with complex and fluctuating conditions, also requires anticipation, awareness of hazards, preparedness, resilience and flexibility, the qualities that those studying high-reliability organizations have sought to capture and articulate. To try to instil these qualities into the next generation of clinicians, patient safety is being incorporated explicitly into both undergraduate and postgraduate training. To aid this endeavour, there has been some work to identify the desirable knowledge, skills, behaviours and attitudes of a safe healthcare practitioner. In surgery and anaesthesia, much work has been done to identify and enhance 'non-technical skills', including communication, stress management, teamwork, decision-making and leadership,[40] which promote patient safety – similar skills are, of course, crucial across all specialities, particularly in the care of older people.

Design (human factors and ergonomics) and technology

Increasingly, design and technology are being used to great effect to improve patient safety, as healthcare learns from the principles of human factors and ergonomics which are so well engrained in other safety-critical industries. These disciplines are concerned with the interaction between humans and the systems in which they work, including perception, cognition, human performance, interaction with technology, teamwork and organizational behaviour. Design of hospital equipment used to be carried out by people at a relative distance from end-users, with feedback occurring only at a late stage or when accidents occurred. Now there tends to be a much more integrated approach, with a substantial and growing literature around evidence-based design. This has led to numerous practical benefits, for example in the re-design of labelling and packaging of medications and anaesthetic and emergency equipment, and in designing hospital environments to reduce the incidence of hospital-acquired infection.[1]

The same principles and ideas can be effective in reducing the incidence of geriatric syndromes in older people in hospital. For example, there is a growing amount of work on the role that design of the hospital environment can play in falls and delirium prevention, in terms of ensuring adequate lighting, noise reduction, orientation boards, suitable hospital beds, appropriate flooring and signage.

Advances in technology can reduce errors by improving communication, providing reminders, making knowledge more readily accessible, prompting for key information, assisting with calculations, monitoring and checking in real time and providing decision support.[41] There are many examples of how technology has helped to counteract the cognitive errors that humans can be prone to making, such as the use of barcodes in blood transfusions. It can also enhance the human qualities of judgement and decision-making, such as with computerized decision support with systems for diagnosis, reminder systems for prevention, systems for disease management and systems for supporting prescribing and drug dosing.[42]

Improving systems of care for older people

Technological advances are also making it possible to redesign systems of care for older people, with the aim of providing more targeted and integrated health and social care. For example, the rapidly growing field of telecare has made it possible for older people with sub-acute problems to be cared for in their own homes, in 'virtual wards', thereby avoiding unnecessary hospital admissions.

In hospital, much effort has been made in recent years to implement new ways of caring for acutely ill elderly patients in order to try to minimize functional

decline during hospitalization and subsequent prolonged rehabilitation. For example, it is now common practice for most hospitals in the UK to have an orthogeriatric service to ensure optimal medical care from admission to discharge of elderly patients who have sustained fractured neck of femurs. Stroke units are another example of how specialist care with focused, immediate rehabilitation and anticipation and swift recognition of complications can improve outcomes and reduce hospital-acquired complications such as functional decline.

In general acute geriatric medicine, it has been shown that providing specialist care environments, with staff who are interested in caring for older people and who have had relevant specialist training, can also prevent the development of the geriatric syndromes in hospital. An example of this are Acute Care of the Elders (ACE) units, in which a prepared environment, interdisciplinary collaborative care, multidimensional assessment, non-pharmacological prescription, medical review, home planning and transitional care all combine to improve a range of outcomes, including improved functional status, lower risk of nursing home placement and higher levels of patient and professional satisfaction with care.[43] This system of care, tailored towards the older person, also leads to a reduction in other errors such as inappropriate prescribing.

Interventions for the geriatric syndromes

There are many well-founded interventions for the prevention and management of geriatric syndromes in hospital.[44] These generally fall into the following categories: risk identification and assessment tools, single- or multicomponent practical interventions, changes to systems of care and educational programmes. Many of these are complemented by, or have been incorporated into, national or international campaigns and guidelines for widespread use. All are most effective if underpinned by strong leadership and robust measurement and reporting systems.

Some examples of commonly used risk assessment tools in the UK are the multitude of available falls risk assessment tools, the Waterlow score for assessing pressure sore risk and the Malnutrition Universal Screening Tool (MUST). There are challenges to the effective use of screening tools such of these: they should be completed by staff who have a sound understanding of the conditions they are assessing and identification of risk must be followed by justifiable actions to prevent the development of the geriatric syndrome.

The best known and most widely used general assessment tool for older people is Comprehensive Geriatric Assessment (CGA). This contains six key elements: assessment of functional ability, cognitive function, physical health, socioeconomic status, nutritional status, mobility and falls risk. Its purpose is to provide a holistic assessment of all issues relevant to a frail patient: it has been shown that if CGA is combined with strong and sustained interventions, better long-term outcomes can be achieved.[45] However, it is unclear whether it has any impact on hospital-acquired complications, although it undoubtedly identifies those who are the most frail and at the highest risk of adverse outcomes.

A good example of a practical intervention designed to prevent the development of a geriatric syndrome in hospital is the multicomponent intervention for delirium tested as part of the Elder Life Program.[46] In this study, six well-known risk factors for delirium (cognitive impairment, visual and hearing impairment, sleep deprivation, immobility and dehydration) were addressed in a comprehensive manner by a trained interdisciplinary team and tested in a controlled clinical trial: the incidence of delirium was reduced from 15% in the 'usual care' group to 9.9% in the intervention group (giving a matched odds ratio of 0.60, with $p = 0.02$). The actual practical methods used in each protocol were simple, commonsense management that it could be argued should form part of 'best practice' and good, empathetic care for all elderly patients. Other multifactorial interventions, when supported by strong leadership and robust measurement and reporting, have been shown to be key to reducing other geriatric syndromes, such as falls.[47]

Hospital-acquired infection

Significant progress has been made in recent years in reducing hospital-acquired infections (HAIs) across all age groups, not just in older people. This has partly been driven by regulatory and public pressure in response to a shift in societal attitudes about acceptable levels of risk, which have made HAIs a major organizational priority and a matter for statutory regulation. HAIs are relatively easy to measure and identify, so the impact of interventions for them can be easily assessed, unlike some of the other hospital-acquired complications common in older people. There are now standard definitions for HAIs, an increasing trend towards mandatory reporting of infections and, in most hospitals, infection control departments which independently monitor and act to reduce HAIs.

The underlying causes of HAIs are complex, ranging from individual actions or inactions, such as failures to follow rules and procedures, through to systemic failures or problems with design and technology. Consequently, many of the interventions which have been successful in tackling HAIs are equally as complex and are increasingly being seen as part of more general quality improvement programmes rather than solutions in isolation. For example, HAIs are one of the major outcome measures of the Safer Patients Initiative,[48] a long-term collaborative programme developed by the Health Foundation in partnership with the US

Institute for Healthcare Improvement and 24 participating UK NHS Trust sites. This ongoing initiative has a focus upon reliability and safety of care through application of continuous quality improvement techniques adapted from process industries and manufacturing.

Some of the other multifaceted interventions which have been shown to reduce the rates of HAIs include the use of care bundles to tackle central line infections and ventilator-associated pneumonias in intensive care units or using combined approaches to improve hand hygiene on general wards. Other effective infection control measures have included advances in treatment, regularly updated antibiotic prescribing guidelines and the use of other precautions such as minimizing ward transfers. Design of the hospital environment has an important part to play, in terms of providing adequate isolation and cleaning facilities and allowing sterile practices to be carried out with minimal contamination. Other innovations include the use of decision support systems in antibiotic prescription or allowing patients to participate in infection control initiatives (although older people may be less willing or able to do this).

Medication safety

Reducing medication error requires a multifaceted approach involving computerized systems, simplification and standardization of clinical processes, education and training and wider cultural and organizational change.[49]

Much work has been carried out to reduce medication error in general. The principles underlying this are common to all successful safety and quality improvement processes: systems must be designed to prevent errors occurring in the first place, then to make errors more visible when they do occur and finally to limit the effects of errors so they do not lead to harm. Standardization of processes, paying particular attention to high-risk medications and involvement and collaboration with both patients and clinicians have all been shown to be successful strategies.

There are several categories of interventions that have been shown to maximize medication safety for older people in particular. Much as for falls or delirium, the first step is to identify and prevent inappropriate prescribing. Assessment instruments such as the Beers criteria, STOPP and START,[50] give lists of drugs to avoid in older patients. These tools are useful for both the prevention and measurement of inappropriate prescribing. The potential drawbacks of such tools are that they may not be internationally useable, they rely on correct usage by prescribers and they may not include all classes of relevant drugs.

A crucial intervention to improve medication safety in older people is medication review and medicines reconciliation, both of which should ideally occur routinely at transitions of care and form a crucial part of specialist geriatric assessment. In primary care, various measures have been shown to improve overall medication safety in older patients, including clinical pharmacist intervention, educational measures and computerized support.[18]

As described earlier, one of the problems in assuring appropriate prescribing for older people is that they have often been excluded from relevant large clinical trials, leading to uncertainty about the safest way to prescribe for them. However, this trend seems to be being reversed of late, with older people being specifically targeted for recruitment into such trials.[31]

Priorities for improving the safety and quality of care for older people

Research priorities

Patient safety in older people across the world

Of course, patient safety is a global priority, of concern to older people and healthcare services all over the world. More research is required to understand the patient safety issues particularly relevant to older people in developing countries.

Improved definitions and measurement

In order to understand and improve safety and quality in older people, particularly those who are frail and complex, it is crucial that we consider further what safety and quality actually mean in this population. As described earlier, existing ways of measuring safety in hospitals, in particular, through case record review or reporting, are not particularly good at detecting the complex geriatric syndromes that are important both to these patients and to the healthcare system. This is not surprising, considering that such measures were not originally developed with the frail older person in mind. Very few adverse events associated with poor clinical reasoning, communication skills or safety awareness are detected by the usual methods of clinical incident reporting.

The complex nature of frail older patients can lead to difficulties when unravelling cause and effect when trying to assess safety in these patients. Another complicating factor is that there are blurred boundaries between adverse outcomes of hospitalization that are not preventable, preventable adverse events and providing a high-quality service.

Current measures of quality of care in older people tend to assess the management of specific clinical problems across healthcare sectors, such as the national audits of stroke, falls and bone health and incontinence in the UK or the ACOVE measures developed in the USA.[51] There is certainly a need to develop generalizable quality indicators for the acutely unwell frail elderly person in hospital, as highlighted recently by the NHS Confederation in the UK.[52]

Patient safety research in non-hospital settings

Much of this chapter has so far concentrated on the hospital environment because that is where the majority of patient safety research has been carried out; of course, although the frailest older people tend to undergo hospitalization the most frequently, they also encounter health services in other settings, most notably in intermediate care, primary care and care homes. Unfortunately, comparatively little research has been carried out on adverse events in older people in these settings, and this needs to be addressed, especially as systems of care are developed to minimize hospital admissions and maximize independence at home for older people. Perhaps the most vulnerable elderly population are those who reside in care homes; here, the patient safety issues are likely to be similar to those encountered in hospital in terms of geriatric syndromes, risks associated with immobility and functional decline and adverse drug events. There are, however, crucial differences likely to affect patient safety in care homes compared with hospital: in this environment things move at a different pace, the majority of patients are frail, responsibilities and expertise amongst staff are different and problems with the management and diagnosis of acute problems will also differ. Although work has been done to look at certain aspects of patient safety in these environments, such as medication safety, there is still much to do.

Key points

- Older people are more vulnerable than younger patients to healthcare-associated harm and its consequences. This tendency is associated with frailty and comorbidity rather than age alone – as our populations age, systems of care need to be designed with this in mind.
- Older people experience a wider range of adverse events than their younger counterparts in hospital – including the geriatric syndromes, yet patient safety in this population is comparatively under-researched.
- There is a need to improve measurement of safety and quality of care in older people and to understand more about patient safety for older people in non-hospital settings.
- Key areas of focus for improving patient safety in older people include the design of safer healthcare systems for older people, the early detection, prevention and management of the geriatric syndromes, providing education to individual clinicians to enhance decision-making, assessment and team working skills and efforts to reduce ageism and negative attitudes towards older people and their care.

Conclusion

In summary, it is clear that although excellent healthcare exists for older people, there are many areas in which further safety and quality improvements can be made for this vulnerable population. As, justly, patient safety and quality of care become the main focus of planners of healthcare services, and with increasing advances in design and technology, it should be possible to make sure that systems of care for older people develop to maximize safety and quality. Continuing attention needs to be paid to the education and training of individual clinicians in respect of the unique decision-making, assessment and team working skills necessary to provide excellent care for older people. We should be particularly mindful of strategies for the early detection, prevention and management of the geriatric syndromes and effective ways of tailoring treatment for the individual. Crucially, safety and quality of care will also be enhanced if the ongoing problems with ageism and attitudes towards older people and their care could be addressed.

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SECTION 1

Eating Disorders and Nutritional Health

CHAPTER 15

Epidemiology of nutrition and ageing

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Introduction

Population ageing is considered one of humanity's greatest success stories. It is also one of the greatest challenges to cope with in socioeconomic and health policies. Worldwide, the proportion of people aged 60 years and over has risen from 8% in 1950 to 11% in 2007 and is expected to reach 22% in 2050.[1] In addition, it is predicted that decreasing fertility rates and increasing longevity will ensure the continued 'greying' of the world's population. Ageing is a complex process and apart from factors intrinsic to the individual, extrinsic and treatable factors also play a role, such as environmental and lifestyle variables.[2] Since extra years in old age are not always spent in good health, the question often is raised, 'How do I get old healthy?' Analyses of the major causes of death clearly show that the burden of chronic diseases has increased rapidly. Most data come from self-reported (co-)morbidity and medical records confirm this trend. Partly this increase may reflect improved medical knowledge and health service use in elderly people. Such progress leads to a longer period of morbidity, but with an improved functional status.[3] Many of the health risk factors are related to nutrition and inactivity and include high blood pressure, high concentrations of serum cholesterol, low intake of fruits and vegetables, being overweight and alcohol and tobacco use. These factors may lead to, amongst others, cardiovascular disease, type 2 diabetes, certain types of cancer and osteoporosis. These global epidemiological data have prompted the WHO (World Health Organization) and FAO (Food and Agriculture Organization) to set up a Joint WHO/FAO Consultation on Diet Nutrition and the Prevention of Chronic Disease. The report of this group provides dietary recommendations, including the following guidelines:[4]

- limit energy intake from fat and shift consumption away from saturated fats and *trans*-fatty acids towards unsaturated fat;
- increase consumption of fruits and vegetables and also legumes, whole grains and nuts;
- limit the intake of 'free' sugars;
- limit salt (sodium consumption from all sources) and ensure that salt is iodized;
- achieve energy balance for weight control.

The guidelines are evidence based for younger adults and more recent research has shown the potential impact in older adults. In old age, frailty is likely to develop (Figure 15.1) and therefore may expand the role of nutrition from the prevention of diseases to the supply of specific nutrients and the maintenance of food intake. This food intake should be sufficient to combat frailty and to maintain quality of life. Frail is defined here as an age-related physiological vulnerability resulting from impaired homeostatic reserve and reduced capacity of the organism to withstand stress.

In view of the desired adaptation of the dietary guidelines to health priorities in older adults, we discuss in this chapter epidemiological evidence for this age group on:

- body weight, body composition and health;
- dietary intake, dietary patterns, diet scores in relation to mortality: differences within and between populations;
- high-risk nutrients;
- determinants of food choice and vulnerable groups;
- effects of nutrition supplements on health indices;
- dietary guidelines in old age.

Body weight, body composition and health

Body weight change, changes in body composition and usual ageing

In cross-sectional studies, the prevalence of high body weight or obesity [body mass index (BMI) $>30\,kg\,m^{-2}$] increases with age up to about 60 years, remains stable until about 70 years and then declines.[6] Studies indicate that both weight loss and weight gain are associated with adverse health outcomes, such as decreased functional status, institutionalization and increased mortality.[7]

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

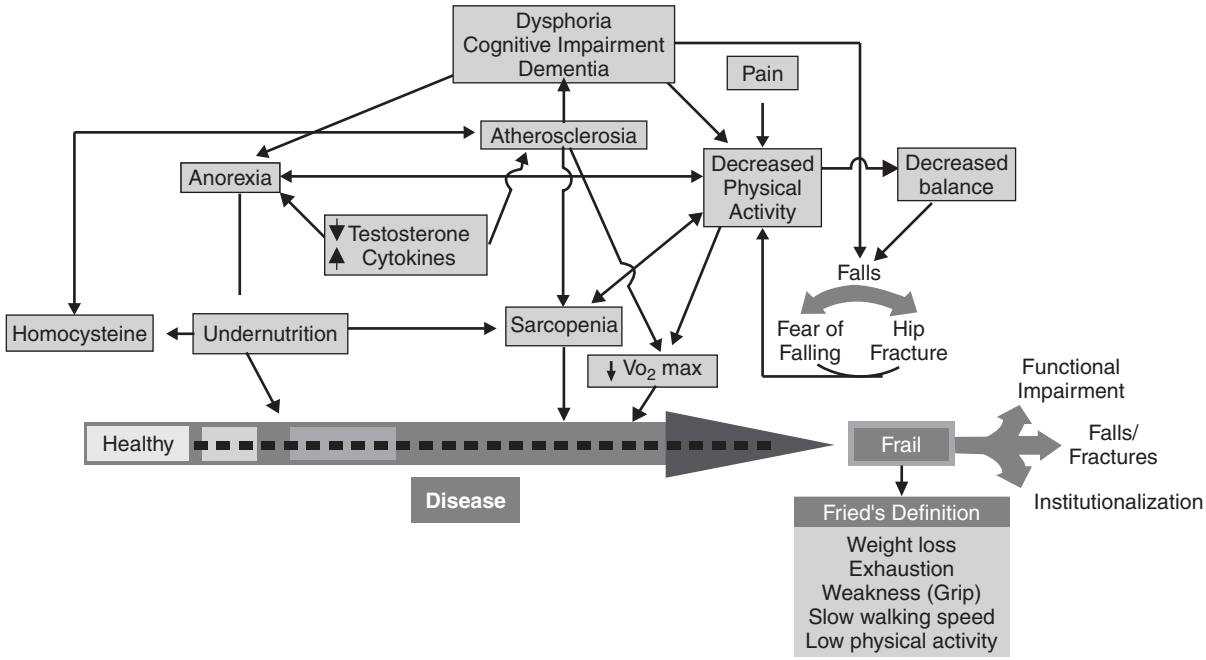

Figure 15.1 The pathophysiology of frailty. (Reproduced with permission from Morley;[5] www.cyberounds.com/conferences/geriatrics/.)

In considering changes in body mass and health, changes in body composition have to be included. A decline in lean body mass occurs in the third decade.[6] This loss in lean body mass, much of which may be due to a sedentary lifestyle, tends to be offset by gains in fat mass that continues until age 65–70 years. At any given BMI, older people will be considerably fatter than younger adults of similar body weight because the fat-free mass diminishes by as much as 70% between the ages of 30 and 70 years. Studies in very healthy elderly people indicate that only very small decreases in weight (0.1–0.2 kg per year) appear to occur in association with normal ageing. Therefore, weight loss should never be dismissed as part of the ageing process.

Most of the studies on BMI in the aged have been conducted in the United States [e.g. the Baltimore Longevity Study, the New Mexico Study and the older age group of NHANES III (National Health and Nutrition Examination Survey)] and in Europe [e.g. SENECA (Survey in Europe on Nutrition and the Elderly – a Concerted Action) and the elderly part of EPIC (European Prospective Investigation into Cancer and Nutrition)]. Available data indicate that demographic changes are even more dramatic in the less developed countries. One study including other demographic groups was the International Union of Nutrition Societies (IUNS) cross-cultural study on 'Food Habits in Later Life'. In this study, people of 70 years and older from communities in Australia, Greece, China, Japan, the Philippines and Sweden were involved. The results showed that on average BMI for Caucasian men and women is about 25 kg m^{-2}, with the highest for Greek women (30 kg m^{-2}). Filipino and Chinese had average BMIs between 20 and 22 kg m^{-2}. The estimated fat mass showed, as expected, a large gender difference with on average 43–50% for women and 25–35% for men, but differences in fat mass between ethnic groups were less striking.[8]

The association between BMI, weight loss and health

Many studies have documented that the relative risks of a high BMI may become less pronounced with ageing. A systematic review and meta-analysis conducted to determine the effect of an elevated BMI on all-cause mortality risk in men and women aged 65 years and over concluded that elderly with overweight (25–29 kg m^{-2}) do not have a significantly increased risk of mortality. A BMI in the obese range (30 kg m^{-2} and over) is associated with only a modest increase in mortality risk regardless of gender, disease status and smoking status.[9] Several explanations for this phenomenon have been put forward, such as selective survival, cohort effects and/or a ceiling effect of mortality rates. The most important explanation might be that BMI is not a good indicator of body composition. The U-shaped relation between BMI and mortality in younger adults may be the result of a positive association between body fat mass and mortality and an inverse linear association between fat-free mass and mortality. As stated above, the ratio between the two compartments (fat and fat-free mass) changes with ageing and the BMI does not measure this. Further, kyphosis in old age makes it difficult to measure height and, therefore,

may result in unreliable estimates of BMI. For this reason, changes in weight (rather than changes in BMI) are a preferable measure, although in the interpretation the possibility of oedema has to be taken into account.[10] As a final reason for the less pronounced relative risk of a high BMI, it is suggested that an excess fat mass is less detrimental in old age. However, recent views on pro-inflammatory factors related to adiposity indicate that fat loss ameliorates some catabolic conditions of ageing since some cytokines may directly affect muscle protein synthesis and breakdown. A voluntary decrease in weight may also ease the mechanical burden on weak joints and muscle, thus improving mobility. Therefore, only weight-loss therapy that minimizes loss in muscle and bone condition is recommended for older obese persons. Especially in the case of sarcopenic obesity, prevention of further loss of muscle mass is urgently required. Sarcopenic obesity is defined as the coexistence of diminished lean mass and increased fat mass).[11]

At the other end of the scale, reflecting body weight, prospective studies have shown that weight loss, a decline in BMI, can be both a marker of and an independent contributor to adverse health outcomes. Involuntary weight loss in elderly subjects is likely to reflect sarcopenia, a loss of lean body mass and particularly muscle mass. Other types of weight loss are cachexia, a disease-related weight loss, and starvation or undereating reflecting loss of mainly fat mass. Weight loss may contribute to the increased mortality, especially if the initial body weight is relatively low. Incidence rates of 5–15% have been reported in studies of involuntary weight loss in community-dwelling older adults.[7] In frail elderly people often dependent on professional care, rates of over 25% up to 40% have been observed. Body weight loss is considered the most important indicator of undernutrition. A loss of 10% in 6 months, 7.5% in 3 months or 5% in 1 month is considered very serious, owing to the direct relationship with morbidity and mortality. Further, nutritional deficits are associated with low energy intake, as is shown in Figure 15.2.[12]

Central adiposity and health

Redistribution of body fat with ageing further limits the applicability of BMI as a risk indicator in older adults. There is evidence in younger adults that those who have the majority of their adipose tissue around their waist (high waist-to-hip ratio) have a higher prevalence of diabetes mellitus, hypertension and coronary artery disease than those who have predominantly hip adiposity. Folsom *et al*.[13] examined the role of body fatness on mortality in a random sample of 31 702 Iowan women aged 55–69 years, followed for 11–12 years. Waist-to-hip ratio was positively correlated with mortality, also after correction for smoking, alcohol and estrogen use. Waist-to-hip ratio is, however, increasingly difficult to interpret with further advancing age. Whereas the waist measures abdominal fatness, hip circumference may also reflect variations in pelvic width and gluteal muscle. In elderly people, narrow hips may reflect peripheral muscle wasting, which may correlate with chronic conditions.

The current literature gives inconsistent answers to the question of how useful it is to measure, in addition to BMI, the waist-to-hip ratio or waist circumference only. So far, except for the oldest age group, the conclusion of Canoy[14] based on current epidemiology may be clinically useful: adipose tissue distribution assessment ideally should provide a single risk estimate that captures the separate effects of abdominal and peripheral adiposity. Although far from perfect, waist-hip ratio or just waist circumference is a simple and inexpensive measure that captures these effects and can help to improve CHD and other chronic disease risk assessments. This conclusion should not stop further research and development of an appropriate protocol for the diagnosis of adipose tissue distribution, including the search into cut-off points for specific ethnic, age and other population groups.

Fluid status and dehydration in the elderly

Older adults are at risk for dehydration because of both reduced fluid intake and increased fluid losses. Even in healthy, successful ageing, there is a reduction in thirst in response to water deprivation, which is evidenced both in a lower self-reported thirst score during dehydration and in ingestion of less water after the dehydration period. Acute weight loss of 3% or more of the body mass or more than 1 kg weight loss per day points to dehydration. It is a common and potentially lethal problem in both institutionalized and community-dwelling elderly people. In hospitals, the mortality rate may be up to 50% in those older adults with dehydration. The most common causes of dehydration are infection, altered level of consciousness, cognitive impairment and use of diuretics. Schols *et al*.[15] concluded that dehydration is a common problem in nursing homes, often due to failures in detection of dehydration and appropriate management. An overload of water and salt is also common and may result in impaired recovery from surgery or perioperative mortality and morbidity. For the elderly, it is advised to take about 1.5 l of fluid per day.

Ageing, bone loss and nutrition

Bone loss commences around the age of 40 years and is on average between 0.5 and 1% per year in men; in women, the rate of bone loss accelerates around the menopause to about 2% per year. When bone density falls below 2.5 SD of the mean bone mineral density (BMD) of young adults, the WHO[16] refers to osteoporosis. The latter is a multifactorial disease and defined also as ‘a systemic skeletal disease

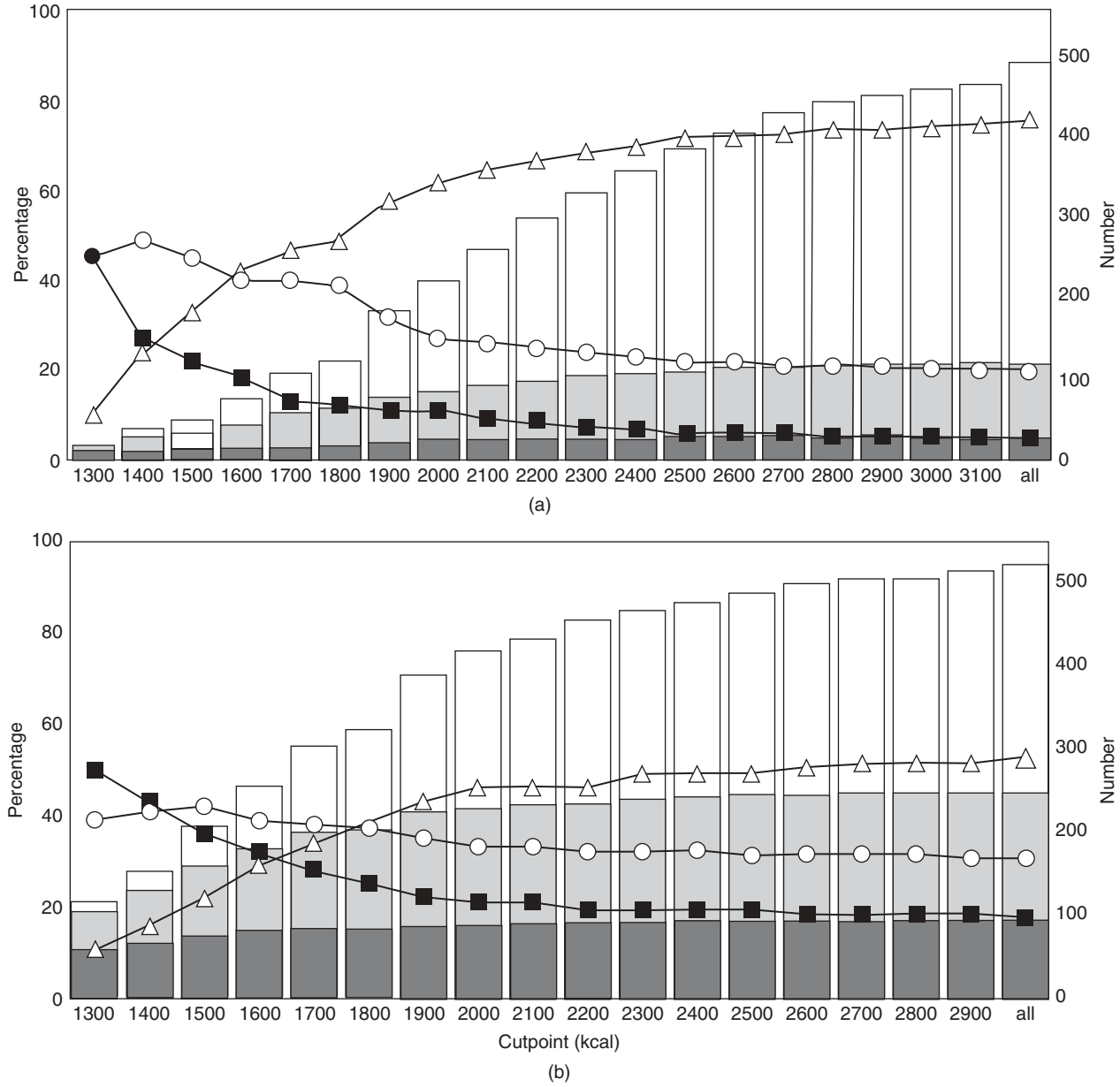

Figure 15.2 Number and percentage of (a) men and (b) women with an inadequate intake of no nutrients (□ and △), one nutrient (□ and ○) and at least two nutrients (■ and □) for groups with energy intakes under different cut points (Reproduced from de Groot *et al.*,[12] by permission of Oxford University Press.)

characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures'. Biological, environmental and genetic factors and also lifestyle factors may play an important role in the onset and development of osteoporosis. The incidence of osteoporosis varies widely between countries and between and within ethnic groups. For instance, the NHANES III study[17] showed that low BMD is most common among elderly non-Hispanic white women (21% osteoporosis) and among Mexican American women (20% osteoporosis) and lower in non-Hispanic black women (18%). In Europe it is estimated that 179 000 men and 611 000 women suffer a hip fracture every year and these numbers are expected to double in the next 40 years.[18]

Although a low percentage of the bone mass can be explained by nutritional factors (less than 20%), it can still have a large impact on bone health. The benefits of supplementation of populations at risk for osteoporosis with vitamin D and calcium are well established in studies with endpoints such as effects on BMD, bone turnover and

a reduced risk of fractures without side affects. The vitamin D requirement may be higher in regions where calcium intake is low. Vitamin D also has a beneficial effect on the risk of falling, explained by an improvement of muscle function. Evidence for associations between optimal protein intake and bone mass is diverse, positive, negative and no associations having all been found. Other dietary factors, such as vitamin K, vitamin A, caffeine, fluoride, phosphorus and zinc, are also subjects of current bone research and it is under debate whether they are important and truly associated with bone health.[19]

Dietary intake, dietary patterns, diet scores in relation to mortality: differences within and between populations

Macronutrients as sources of energy

Population-based nutritional surveys have shown a gradual decline in energy intake in old age. Shifts in the percentage of energy coming from various macronutrients while ageing are less clear. Between populations, the macronutrient composition appears to vary considerably. Across studies, intakes range from 12 to 18% energy from protein, from 20 to 42% energy from fat and from 38 to 65% from carbohydrates.[8] In a background paper, Prentice[20] considered the extent to which the development of recommendations for dietary energy needs to account for the macronutrients. He discussed the issue with a view to avoiding undernutrition in addition to obesity. He concluded that 'at the metabolic level, only diets with the most extreme macronutrient composition would have any consequences by exceeding the natural ability to modify fuel selection. However, diets of different macronutrient composition and energy density can have profound implications for innate appetite regulation and hence energy consumption'. The Omni-Heart study,[21] a randomized three-period cross-over feeding trial, studied self-reported appetite and selected fasting hormone levels by comparing the effects of three diets, each rich in a different macronutrient. It was concluded that a diet rich in protein from lean meat and rich in vegetables reduces self-reported appetite when compared with diets rich in carbohydrate and unsaturated fat. The observed pattern of hormone changes, however, did not explain the inverse association between protein intake and appetite.

Proteins

The role of proteins in the diet is currently being extensively studied and discussed, not only because of the satiating effect. Alterations in the ability of cells to regulate homeostasis underlie the pathogenesis of severe human diseases. Even in the absence of disease, deterioration of protein homeostasis likely contributes to different aspects of 'normal ageing'. This makes it difficult to formulate evidence-based requirements for proteins in the diet of (frail) elderly people. There is general agreement on moderately increasing protein intake above 0.8 g kg^{-1} body weight in the elderly (up to 1.5 g kg^{-1}), which may help to reduce progressive loss and stimulate muscle protein anabolism. Current gaps in our understanding of altered protein homeostasis in ageing urgently require further studies.[22]

Dietary patterns and diet scores

In nutritional epidemiology, recently there has been great interest in assessing the relationship between dietary patterns and health, rather than the relation with single nutrients. The reason is that foods and nutrients are interrelated and people do not eat single nutrients, but foods. To investigate dietary patterns, two common methods used are cluster analysis and calculation of diet scores. Cluster analysis explores the categorization of persons into groups on the basis of similarity in food intake (e.g. alcohol drinkers or fish and grain eaters). Diet scores are based on dietary guidelines and are applied to identify groups with good or poor nutritional status. In the United States and Europe, existing measures of overall dietary quality include the Healthy Eating Index (HEI), Mediterranean Diet Score (MDS) and the Healthy Diet Indicator (HDI). These diet scores differ in diet components, scoring rates and definition of cut-off values (Table 15.1).

In spite of these differences, both diet scores and cluster analysis have been shown to be useful tools in identifying groups with different nutritional status. Haveman-Nies *et al*.[23] evaluated the dietary quality of European and American elderly subjects using cluster analysis, the healthy diet indicator and two versions of the MDS. These measures were tested for associations with lifestyle and nutritional status in an elderly population aged 70–77 years from the Framingham study and from the SENECA. Table 15.2 shows food group intake and results of the scores by the five dietary pattern clusters observed.

In general, Southern European centres and Framingham had better mean diet scores than Northern European centres. Cluster analysis revealed that the meat, eggs and fat pattern coincided with significantly lower average dietary quality, as measured with all three scores, compared with all other clusters except the alcohol cluster. The cluster characterized by a relatively high fish and grain intake had a significantly better MDS than all other clusters. High-quality diets were associated with less body fatness, greater physical activity and non-smoking.

Sofi *et al*.[24] (2008) confirmed in a meta-analysis a favourable effect of a Mediterranean type of diet and found a reduction of 9% in overall mortality, mortality from

Table 15.1 Main items in three diet scores: Healthy Eating Index (HEI), the Mediterranean Diet Score (MDS) and the Healthy Diet Index HDI.

HEI[a]	MDS[b,c]	HDI[d]
Grains	Cereals	Complex carbohydrates, dietary fibre, mono- and disaccharides
Vegetables	Vegetables	Vegetables and fruits
Fruits	Fruits and nuts Legumes Alcohol	Pulses, nuts, seeds
Meat, poultry, fish, eggs, dry beans, nuts	Meat and meat products	Protein
Milk	Dairy and dairy products	
Energy: % of: Total fat Saturated fat	Ratio monounsaturated/saturated fat	Ratio saturated/polyunsaturated fat; cholesterol
Salt intake		
Variation score		

[a]For calculations of the index, see http//www.cnpp.usda.gov.
[b]Recently, this score has been changed with alcohol as a separated recommendation and fish introduced in the core pyramid. Also, daily physical activity obtains attention. Oldways Preservation and Exchange Trust 1999 to 2003.
[c,d]For calculation of the score, see Haveman-Nies *et al*.[23]

cardiovascular diseases (9%), mortality from cancer (6%) and incidence of Alzheimer's disease (13%). Additionally, two prospective studies suggested that adherence to the Mediterranean diet may not only affect the risk for Alzheimer's disease, but may also slow the disease and reduce the risks of mild cognitive impairment.

In the elderly part of the EPIC study, it was explored how each individual component of the Mediterranean diet contributes to the observed effects. Several of the components appeared to reduce mortality risk, but most clearly a general plant-based diet, correlating well with the Mediterranean diet ($r = 0.62$), was associated with lower all-cause mortality in elderly Europeans in the EPIC study.[25]

Daily meals and other lifestyle factors

The number of meals eaten per day and the consumption of snacks between meals can differ widely between populations. The SENECA study showed large differences in the number of meals eaten per day, with median ranges from six in Denmark to three in the South of France. Meal-based nutrient intake data suggest that the cooked meal in the southern Europe mediates the beneficial effects of the Mediterranean diet. Knoops *et al*.[26] showed that in addition to adherence to daily meals and a Mediterranean diet, other healthy practices are important, such as not smoking, moderate alcohol use and physical activity (Figure 15.3).

Determinants of food choice and vulnerable groups

It is generally recognized that food choice may be affected by biological factors (hunger, appetite and taste), economic elements (cost, income and availability of foods), structural elements (access, education, cooking facilities, skills and time), social characteristics (culture, family, peers and meal patterns) and further attitudes, beliefs and knowledge about food. Clearly, changes in these factors may change food habits and in the aged population it often may lead to a less favourable diet. Age-related energy reduction can be explained by physiological factors such as a lower metabolic rate and less mobility. When these factors coexist with both a decrease in the need to eat and a decrease in the pleasure in eating it, it may predispose to malnutrition.

Fjellström[27] reported that within older populations, there are some subgroups such as socially isolated, lonely, institutionalized and economically deprived people who are more likely to be consuming an unbalanced diet. Early studies have shown that among older persons aged 60–94 years, loneliness and social isolation were related to dietary inadequacies. Food consumption data for elderly people living alone, however, did not show an adverse impact either in the United States or in Europe.

Locher *et al*.[28] found that ethnicity and gender were risk factors for older people's food consumption. Older black women were most at risk followed by older black men and older white women. They concluded that what contribute most to nutritional risk are social isolation, low income level, limited support and social capital, including transportation to food shops and congregated meal sites, and also limited independent life span.

Institutionalized elderly people tend to have a lower energy intake – mainly due to a lower fat intake – and a lower protein intake. Furthermore, nutrient inadequacy is more prevalent in the institutionalized elderly than in community-dwelling groups. At the same time, no clear differences in food patterns were observed. Therefore, the main cause of the higher prevalence of nutrient inadequacy in dependent elderly people is most likely the low level of total food intake. An exception might be the group with a poor state of dentition. In both the NHANES III and SENECA studies, a lower quality of the diet was observed due to avoidance of food groups such as meat, fruit and vegetables. Comparative observations come from a sample of low-income households in the UK.[29]

Table 15.2 Mean (SD) food group intake of 70–77-years elderly of the Framingham Heart Study and SENECA's baseline study, by dietary pattern cluster.

	Sugar (*n* = 526)		**Fish and grain (*n* = 307)**		**Meat, eggs, and (*n* = 659)**		**Milk and fruit (*n* = 525)**		**Alcohol (*n* = 93)**	
Northern centre (n) (total = 782)	101		18		511		129		23	
Southern centre (n) (total = 500)	28		187		55		191		39	
Framingham, MA (n) (total = 828)	397		102		93		205		31	
Energy (MJ)	8.0	(2.5)	8.0	(3.1)	8.7	(2.5)	7.6	(2.6)	9.1	(2.7)
Energy (kcal)	1911	(605)	1903	(735)	2084	(595)	1826	(613)	2185	(641)
Food/nutrient groups (g):										
Grains	172	(86)	310	(176)	183	(80)	169	(92)	171	(93)
Alcoholic beverages	61	(100)	99	(159)	126	(176)	74	(129)	911	(423)
Milk and milk products	200	(169)	218	(175)	289	(213)	403	(293)	142	(147)
Fruit and fruit products	179	(129)	216	(149)	163	(126)	349	(251)	165	(148)
Eggs	12	(11)	10	(11)	18	(22)	10	(11)	15	(15)
Meat and poultry	97	(46)	87	(48)	142	(63)	92	(53)	103	(57)
Fish/shellfish	26	(21)	58	(43)	24	(24)	42	(49)	46	(52)
Vegetables	261	(131)	217	(138)	287	(132)	294	(191)	256	(143)
Total fat	70	(30)	59	(27)	96	(35)	65	(28)	66	(28)
Legumes/nuts/seeds	29	(28)	13	(16)	7	(12)	17	(20)	17	(24)
Sugar and sugar products	94	(68)	28	(24)	44	(34)	34	(35)	42	(50)
Diet scores:										
Healthy diet indicator	3.4	$(1.3)^b$	3.4	$(1.3)^b$	2.4	$(1.1)^a$	3.4	$(1.3)^b$	3.2	$(1.3)^b$
Greek mediterranean diet score	2.8	$(1.3)^b$	3.3	$(1.2)^c$	2.1	$(1.2)^a$	2.9	$(1.3)^b$	2.2	$(1.2)^a$
FS-mediterranean diet score	4.2	$(1.4)^b$	4.6	$(1.2)^c$	3.1	$(1.3)^a$	4.1	$(1.5)^b$	3.4	$(1.2)^a$

^{a,b,c}ANOVA followed by the multiple comparison test was used to test differences in diet scores between dietary clusters. Means within rows with different letter superscripts ($c > b > a$) are significantly different, $P \leq 0.05$.
Source: Reproduced with permission from Haveman-Nies *et al.*[23] Copyright Nature Publishing Group.

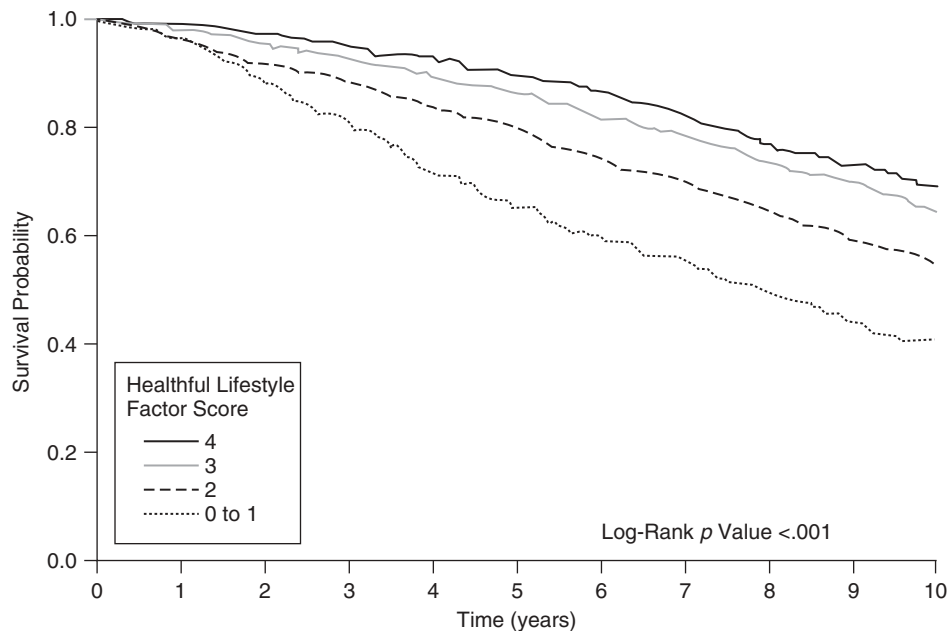

Figure 15.3 Healthful lifestyle scores and the relation with 10 year survival in community-dwelling, elderly Europeans ($n = 2339$). The lifestyle score was calculated by adding the individual scores for diet, physical activity level, smoking status and alcohol intake.[26] (Reproduced with permission from Knoops *et al.*[26] Copyright © 2004 American Medical Association. All rights reserved.)

Institutionalized people are often frail and suffer from both functional and cognitive impairment. In addition to an overall inadequate food intake, several studies have pointed to more specific nutrients and functional decline. Below we discuss some specific high-risk nutrients not directly related to a low energy intake.

High-risk nutrients

An inadequate supply of vitamin B_2, vitamin B_6, folate and/or vitamin B_{12} causes hyperhomocysteinaemia. Homocysteine is considered an independent risk indicator of cardiovascular diseases. Prospective studies also suggest a correlation between elevated homocysteine and dementia and osteoporotic fractures Supplementation with folate and less so with cobalamin or pyridoxine demonstrated a reduction in serum homocysteine. So far, trials have not been conducted or are inconclusive in demonstrating a reducing effect on the incidence of cardiovascular disease, dementia or osteoporotic fractures.

Vitamin B_2 contributes to hyperhomocysteinaemia, but is generally not considered as a high-risk nutrient in elderly people consuming sufficient dairy products.

Vitamin B_6 comprises various derivatives of pyridine, including pyridoxine, pyridoxal and pyridoxamine. There are many dietary sources and therefore dietary deficiency is rare. Vitamin B_6 deficiency usually occurs in association with other water-soluble vitamins. Deficiency may result from alcoholism, malabsorption and other factors such as dialysis. Medication may act as pyridoxine antagonist.

Folate represents a group of related pterin compounds; more than 35 forms of the vitamin are found naturally. The various dietary sources include, in addition to plant sources, also liver and other organ meats. Folate in foods is destroyed by excessive cooking; as much as 95% may be lost.[30] Studies have revealed that folate deficiency may range from 2.5 to 34% in the elderly. Causal factors in addition to poor intake and absorption are atrophic gastritis, excessive alcohol intake, smoking and use of some drugs.

Vitamin B_{12} is a group of cobalamin compounds with a corrin ring and a cobalt atom in the centre. Vitamin B_{12} is available only from animal foods. In the SENECA study, ~25% of the participants had a low vitamin B_{12} status: in some, 25% plasma cobalamin levels were $<260\ \text{pmol}\,\text{l}^{-1}$ and plasma methylmalonic acid (MMA) $>0.32\ \mu\text{mol}\,\text{l}^{-1}$.[7] These levels could be only partly explained by insufficient dietary intake or atrophic gastritis. Pernicious anaemia, terminal ileal resection, bacterial overgrowth and use of specific drugs are other possible causes of a deficiency state.

Vitamin C (ascorbic acid) is a water-soluble vitamin widely found in fruits and vegetables. Unfortunately, this vitamin is readily lost from foods during storage and preparation. Such losses may account for about 50% of the potential vitamin content in the total diet. For Dutch and Danish diets, such vitamin C losses amounted to ~45% of the vitamin C content of the diet and, consequently, ~30% of the subjects had too low intakes. Results from the NHANES III study showed that average intake serum levels were normal in Americans, but smokers, those not taking supplements and non-Hispanic black males had higher risks. Low serum levels for the last group were mainly due to low intakes of fruits and vegetables.[31] Older people who make use of catering or restaurant facilities on a daily basis are at particular risk for insufficient vitamin C intake, the reason often being the long distance of carrying prepared dishes from the kitchen to the place of consumption. The absorption of the vitamin seems not to be affected by age. Low vitamin C levels have been associated with, in addition to classical deficiency signs, increased risk of coronary artery disease and senile cataract. The mechanism behind it is most likely the antioxidant properties of vitamin C.

The term vitamin A refers to a family of molecules containing different functional groups on a cyclohexenyl group and include retinol, retinal, retinoic acid and retinyl ester. Dietary sources are mainly retinyl esters provided by animal-derived foods. Plant foods supply vitamin A as carotenoids such as β-carotene, α-carotene and β-cryptoxanthin. Vitamin A is of worldwide concern as a risk nutrient, but has not been observed as a specific problem for elderly people, probably due to lower requirements in old age.[32] An exception might be the observations of very low intakes in some ethnic groups in Asia.[8]

Vitamin D (calciferol) refers to a group of lipid-soluble compounds with a four-ringed cholesterol backbone. Vitamin D is not considered a true vitamin, because the human body can synthesize it with adequate sunlight exposure. In most cultures, about one-third of the vitamin D requirements can be obtained from a diet of fish, meat and milk fat; the remainder has to be synthesized. As a result of limited sunlight exposure and a fourfold reduced capacity of the skin to produce vitamin D, deficiencies occur especially in homebound elderly people. Nevertheless, in the relatively healthy older European participants of the SENECA study, 40% had serum hydroxyvitamin D levels below $30\ \text{nmol}\,\text{l}^{-1}$,[7] and this latter standard is below the currently proposed level of at least $50\ \text{nmol}\,\text{l}^{-1}$.[33] Vitamin D supplementation results in decreased bone loss and fracture rate in both older men and women. More recent trials also indicate improvement of sarcopenia and a decrease in falls.

Calcium is related to bone health and is a risk nutrient in elderly people with no or little dairy products in their diet. This might happen within many cultures and was particularly observed in some Asian centres.[8] It is not, however, specifically an age-related problem.

Zinc deficiency is not rare in older persons, particularly among diabetics. Zinc is available widely in foods but

the bioavailability is better from animal than plant foods. In whole grain products, phytates may inhibit absorption. Red meat, seafood, fresh fruit, vegetables and dairy products are the main sources. Zinc is involved in protein synthesis, nucleic acid synthesis and gene regulation. Further, it is part of several enzymes. Biochemical abnormalities of zinc deficiency include a reduction in plasma zinc concentrations, protein synthesis, activity of metalloproteins, resistance to infection, collagen synthesis and platelet aggregation. Other manifestations of zinc deficiency are anorexia due to impaired taste and smell, impaired vision, confusion and restlessness and sometimes diarrhoea. Zinc measurements are often problematic. Cytokines dramatically reduce serum zinc. Leukocyte zinc levels or zinc hair levels when determined properly may be useful.

Iron has special nutritional interest because of the high incidence of iron deficiency worldwide in younger age groups. Iron is available in many foods in small amounts, but between foods the bioavailability differs considerably. Two broad categories of iron are present in food: haem iron derived mainly from animal foods and non-haem iron in plant foods. Haem iron is much better absorbed. Because of this difference in biological availability, dietary recommendations vary according to the nature of the diet. These recommendations are difficult to meet in diets with a low bioavailability. However, the requirement is sharply reduced in postmenopausal women and their iron status is correspondingly improved. Adult men generally have no problem in meeting their iron requirement. When anaemia is diagnosed, chronic blood loss or deficiency of folate or vitamin B_{12} should be considered. In the elderly using multi-supplements, concern about the iron status should rather be with the avoidance of overexposure than with the prevention of deficiency. To determine iron status, serum iron together with ferritin should be determined. In some cases, measuring soluble transferring receptors may be useful.

Effect of nutritional supplements on health indices in frail elderly people

There are many ways to improve the nutritional situation in old age, mostly aimed at improving nutrient intake in terms of either quantity and or quality. In order to assess the efficacy of nutrition-related interventions in the frail elderly, a number of studies, reviews and meta-analyses have been conducted.[34] The supplements studied varied in composition and also outcome measures. Nevertheless, the results of the studies are more or less in the same direction. Improvement of body weight has been reported, which could be fat, muscle or water. However, a gain in fat mass or water will not improve muscle strength. Most likely a combination with exercise is necessary to improve muscle strength and function. Further, most studies show improvement of biochemical parameters of the nutritional status, such as serum vitamin levels and functional biochemical parameters, for example, serum homocysteine. Beneficial effects were more convincing when the intervention was conducted during a longer period and when the patients had more serious functional impairments.

A literature search indicated that in frail elderly people, a combination of macronutrients and micronutrient (enriched or fortified foods) might be preferred. Such an intervention affects several aspects of the nutritional and health status of this group. The doses should not exceed the recommended daily intakes, because adverse affects of such doses on organ systems have been reported.[35] As stated before, older people are very heterogeneous, with different diagnoses, as reflected in the trials. Some patient groups may be more likely to benefit than others. For instance, patients with hip fractures and who are often undernourished when admitted to hospital may profit more from supplementation than those admitted after stroke and who are less undernourished. More work is required to understand better the mechanisms by which extra nutrient supply can affect patients with different chronic and acute conditions.

Milne *et al*. reported that collected data were limited by the poor quality of most included trials.[35] Trials should have sufficient statistical power and length of follow-up to detect any beneficial effects, have properly concealed allocation and, where possible, blinding. Including outcomes of relevance to patients, such as improvement of functionality and/or quality of life, may help sure better compliance. Owing to the effects of gastrointestinal disturbances, for instance nausea, vomiting or diarrhoea, poor appetite or poor taste of the supplement, compliance might be very low.[36]

For improvement of dietary intake not only supplements may help. Nijs *et al*. showed that simple measures such as providing family-style mealtimes in a comfortable dining room with nicely set tables and choice of cooked food and friendly attentive staff prevented a decline in quality of life, physical performance and body weight decline in nursing home residents.[37] In a cross-sectional descriptive study, preferences for improvement of intake by the elderly were analysed. Out of 15 forced-choice comparisons, food quality improvements, feeding assistance and the provision of multiple small meals and snacks throughout the day were the strongly preferred approaches, as opposed to nutritional supplementation.[38]

Dietary guidelines

In this chapter, we started with the WHO dietary guidelines for the prevention of chronic diseases.[4] Epidemiological studies on nutrition and ageing show that the guidelines for elderly people are very similar to those formulated for

younger adults. However, the priorities should be different. First, it is recommended to aim for stable body weight and maintenance of fat-free mass by sufficient physical activity. When the energy requirement decreases, the need for nutrient-dense foods, as comprised in the healthy diet index or MDS score, should be included. Further sufficient fluid (although the recommended 1.5 l is a maximum rather than an average) is important and, as indicated earlier, attention should be paid to some supplements. For vitamin D, there is sufficient evidence that a supplement is required for groups of elderly people. Homebound elderly people are most at risk. In addition, for elderly people with insufficient intake of dairy products, extra calcium is required and elderly people suffering from atrophic gastritis may benefit from a vitamin B_{12} supplement.

Frail elderly people with a very low energy intake may need enriched or fortified foods with vitamins and minerals added according to the dietary recommendations.

In conclusion, although there are still many questions regarding the relationship between dietary patterns and health and in the effectiveness of supplement use, the epidemiology of nutrition and ageing supplies us with sufficient evidence about the importance of adequate nutritional care and a healthy diet in old age.

Key points

- The relative risks of a high BMI become less pronounced with ageing. If weight loss therapy is indicated in obese elderly, it should result in a minimum loss of lean body mass, especially in sarcopenic obese elderly people.
- A low energy intake (<6.3 MJ/1500 kcal) goes together with an insufficient supply of micronutrients. Therefore, in frail elderly people the focus with meals should be on tasty, nutrient-dense foods.
- Also in an elderly population, healthy dietary patterns are related to decreased total mortality and disease-specific mortality.

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CHAPTER 16

The anorexia of ageing

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The 'paradox' of undernutrition in older people

Overnutrition is the major form of malnutrition in the developed world. A substantial proportion of older people in western countries are overweight or obese according to generally accepted body mass index (BMI) [weight (kg)/height (m^2)] criteria. For example, in a 2000 study, 58% of Americans aged ≥65 years had a BMI of 25 kg m^{-2} or more,[1] the World Health Organization cutoff for overweight. Weight loss is usually recommended for overweight and obese older adults in the same manner as in younger adults. and at any given time a substantial proportion of older people wish to lose weight. Furthermore, there is evidence from studies in species as varied as yeast, spiders, mice and possibly primates that long-term restriction of energy (food) intake by 30–60% compared with *ad libitum* intake prolongs life.[2] It might seem, therefore, that reduced food intake leading to weight loss would be good for the majority of older people. This is not necessarily the case, however. The effects of long-term voluntary energy restriction have not been tested in humans and the benefits observed in other species may not apply to ours. Even if such a restriction is beneficial, it may have to be started in childhood,[3] with consequent inhibition of normal growth. Marked energy restriction in older adults is likely to lead to a substantial loss of beneficial lean body tissue and also fat mass and increase the risk of vitamin, mineral and other dietary deficiencies. Calorie restriction in older adults should be considered 'experimental and potentially dangerous'.[3]

As indicated in the following text, (1) ideal weight ranges are almost certainly higher in older than young adults; (2) weight loss is often associated with adverse effects in the elderly, particularly if unintentional; and (3) undernutrition manifesting as low body weight and weight loss is common in older people and has significant adverse effects. For these reasons, caution should be exercised in recommending weight loss to people aged over 70 years and a high level of awareness needs to be maintained to detect unintentional weight loss and undernutrition in this age-group.

'Ideal' body weight in older people

There is increasing evidence that the adverse effects of being overweight or obese, as defined by standard BMI criteria, are not as great in the elderly as in younger adults. Ideal weight ranges based on life expectancy are higher for older than young adults. For example, in a 12 year study of 324 000 people in the American Cancer Society Cohort, for people under the age of 75 years there was a significant and progressive increase in subsequent mortality as baseline BMI increased above 21.9 kg m^{-2}. These adverse effects of increasing body weight diminished, however, with increasing age above 45 years and were absent altogether over 75 years.[4] Among 4736 people aged 60 or more followed for an average of 4.5 years in the Systolic Hypertension in the Elderly Program (SHEP),[5] those whose baseline BMI was in the lowest quintile (<23.6 kg m^{-2}) had the highest subsequent mortality and those within the highest BMI quintile (≥31 kg m^{-2}), corresponding to the conventional criteria of obesity, had the lowest mortality.

Recommendations for ideal weight ranges in older people vary, but there is good evidence that BMI values below about 22 kg m^{-2} in people over 70 years of age are associated with worse outcomes than higher weights, and BMIs below 18.5 kg m^{-2} are a particular concern. The optimum BMI for survival in people over age 70 years is probably in the range 25–30 kg m^{-2} and there is some recent evidence that BMIs above (so-called) normal may be somewhat more protective in women than men.[6]

Although optimum body weight for older people is probably higher than that for young adults, they in fact tend to weigh less. The decline in body weight with age, as measured by BMI, has been well documented in population-based, cross-sectional and longitudinal

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studies.[7,8]. For example, in the 1997–1998 US National Health Interview Survey of 68 556 adults, more people aged 75 years and older than those aged 45–64 years were 'underweight' (BMI <18.5; 5 vs 1.2%) and substantially less were 'overweight' (BMI >25; 47.2 vs 63.5%).[7]

Weight loss in older people

The lower average body weight of older than younger adults is not just because overweight people die earlier from obesity-related diseases, leaving the healthy, thin people behind. On average, people over 75 years of age are more likely to lose than gain weight,[9,10] in part explaining why they weigh less than younger adults. For example, in a study that followed 247 community-dwelling American men aged over 65 years for 2 years, on average these men lost 0.5% of their body weight per year and 13.1% of the group had involuntary weight loss of 4% per annum or more.[9] Numerous studies have shown that weight loss in the elderly is associated with poor outcomes, certainly if involuntary, but possibly even when deliberate. The prospective Cardiovascular Health Study[10] for example, studied 4714 home-dwelling subjects aged over 65 years without known cancer. In the 3 years after study entry, 17% of the subjects lost 5% or more of their initial body weight, compared with 13% who gained 5% weight or more. The weight-loss group had significant increases in total [2.09 × ↑ (95% confidence interval (CI) 1.67–2.62)] and risk-adjusted mortality [1.67 × ↑ (95% CI 1.29–2.15)] over the following 4 years compared with the stable weight group. The increased mortality occurred irrespective of starting weight and whether or not the weight loss was intentional. The weight gain group had no increase in mortality. In the SHEP study mentioned above,[5] those subjects who had a weight loss of 1.6 kg per year or more experienced a 4.9 times greater death rate (95% CI 3.5–6.8) than those without significant weight change. Although mortality was also increased if weight increased more than 0.5 kg per year, the increase was less than that with weight loss (2.4-fold vs 4.9-fold increase). Of particular note, the adverse effects on mortality of weight loss were present even in the subjects who were heaviest at baseline (BMI ≥31) and were independent of baseline weight. The combination of initially low body weight and weight loss is especially bad news for older people. In the SHEP study,[5] subjects with a low baseline weight (BMI<23.6 kg m^{-2} who lost more than 1.6 kg per year had a mortality rate of 22.6%, almost 20 times greater than the mortality rate of those with a baseline BMI of 23.6–28 kg m^{-2} whose weight remained stable. This interaction is a particular concern as the tendency for older people to lose weight is variable, with lean individuals probably most at risk.[11] In an older person, unintentional weight loss of 5% or more over 6–12 months is associated with an increased risk of adverse effects, and a loss of 10% or more very likely means protein-energy malnutrition. There are many reasons why weight loss in older people has adverse effects. It some cases, weight loss is due to an illness, such as a malignancy, which is mainly responsible for the poor outcome and the weight loss is partly an 'innocent bystander'. Nevertheless, the weight loss and associated undernutrition are themselves often a significant problem. This is because loss of body weight after the age of 60 years is disproportionately of lean body tissue, that is, sarcopenia,[12] and individuals lose up to 3 kg of lean body mass per decade after the age of 50 years. Unlike loss of fat tissue, such a loss of lean tissue has adverse effects. Sarcopenia is associated with metabolic, physiological and functional impairments and disability, including increased falls and increased risk of protein-energy malnutrition.

Cachexia in older people

Weight loss and resulting adverse outcomes in older people may be due to cachexia, malnutrition, the physiological anorexia of ageing or some combination of these factors. Although there is often considerable overlap between them, cachexia and malnutrition are not the same. Whereas all cachectic patients are malnourished, not all malnourished patients are cachectic.[13] Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia in adults is weight loss, but inflammation is a key component. Anorexia, insulin resistance and increased muscle protein breakdown are also frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism.[14] Inflammation plays a major role in the pathogenesis of cachexia, with an absolute or relative increase in levels of inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-1 and interleukin-6.[13] Conditions which often afflict older people which are frequently associated with cachexia include cancer, cardiac failure, chronic obstructive pulmonary disease and chronic renal failure. Recently, the European Society for Clinical Nutrition and Metabolism subclassified cachexia on the basis of severity into cachexia and pre-cachexia, the latter being present when there is (1) an underlying chronic disease, (2) a systemic inflammatory response, (3) anorexia and (4) unintentional weight loss over the previous 6 months of less than 5% of usual body weight.[13]

Undernutrition in older people

Prevalence

Protein-energy malnutrition is common in the elderly. Reported rates vary, in part because of differing methods

used to diagnose this condition, but studies in developed countries have found that up to 15% of community-dwelling and home-bound elderly, between 23 and 62% of hospitalized patients and up to 85% of nursing home residents suffer from the condition.[15]

Adverse effects

Protein-energy malnutrition is associated with impaired muscle function, decreased bone mass, immune dysfunction, anaemia, reduced cognitive function, poor wound healing, delayed recovery from surgery and ultimately increased morbidity and mortality (see Table 16.1). Epidemiological studies have demonstrated that protein-energy malnutrition is a strong independent predictor of mortality in elderly people, regardless of whether they live in the community or in a nursing home, are patients in a hospital or have been discharged from hospital in the previous 1–2 years.[16] The increased mortality rate in elderly people with protein-energy malnutrition is further increased in the presence of other medical diseases, such as renal failure, cardiac failure and cerebrovascular disease. For example, the 9 month mortality rate of 205 patients aged >70 years without cancer, admitted to a medical ward in Sweden, was 18% in 164 well-nourished patients without cardiac failure, 44% in 41 malnourished patients without cardiac failure, but 80% in 10 malnourished patients with congestive heart failure.[16]

Table 16.1 Effects of weight loss and protein-energy malnutrition on function in the elderly.

↓ Muscle function
↓ Muscle relaxation
↓ Muscle mass
↓ Muscle strength
↑ Risk of fracture
↓ Bone mass
↑ Incidence of falls
↓ Functional status
Immune dysfunction
↑ Increased risk of infection
↓ Delayed skin hypersensitivity
T-cell lymphocytopenia
↓ Synthesis of interleukin-2
↓ Cytolytic cell activity
↓ Response to influenza vaccination
Anaemia
Poor wound healing
Fatigue
Pneumonia
Delayed recovery from surgery
↓ Cognitive function
↓ Cardiac output
↓ Intravascular fluid (dehydration)
↑ Incidence of pressure sores
↓ Maximal breathing capacity
↑ Hospital admission and length of stay
↑ Mortality

Causes of undernutrition in older people

Reduced food intake

Ageing is associated with a decline in energy (food) intake. Energy intake decreases by ~30% between age 20 and 80 years.[17] Elderly people on average consume smaller meals more slowly, and fewer snacks between meals,[15] and consistently report that they are less hungry than young adults.[18] For example, the 1989 cross-sectional American National Health and Nutrition Examination Survey (NHANES III) study reported a decline in energy intake, between the ages of 20 and 80 years, of 1321 cal per day in men and 629 cal per day in women,[19] a 7 year New Mexico longitudinal study of 156 persons aged 64–91 years reported a decrease of 19.3 kcal per day per year in women and 25.1 kcal per day per year in men[20] and a Swedish 6 year longitudinal study of 98 people found that between the ages of 70 and 76 years there was a decrease in energy intake of 610 cal per in men and 440 cal per day in women.[21]

The physiological 'anorexia of ageing'

The age-related decline in food intake is not just due to the effects of illnesses that become more frequent with increasing age. Numerous studies have documented an age-related decline in appetite and energy intake in healthy, ambulant non-institutionalized people.[17] Healthy older persons are less hungry and are more full before and become more rapidly satiated after eating a standard meal than younger persons. Much of this decrease in energy is probably a response to the decline in energy expenditure that also occurs during normal ageing. In many individuals, however, the decrease in energy intake is greater than the decrease in energy expenditure, so body weight is lost (see the preceding text). This physiological, age-related reduction in energy intake has been termed *anorexia of ageing*.[15]

Loss of homeostasis

Old age is associated with diminished homeostatic regulation of many physiological functions, including the regulation of energy intake. For example, Roberts *et al*.[22] underfed 17 young and old men by 3.17 MJ per day (~750 kcal per day) for 21 days, during which time both the young and old men lost weight. After the underfeeding period, the men were allowed to again eat *ad libitum*. The

young men ate more than at baseline (pre-underfeeding) and quickly returned to normal weight, whereas the old men did not compensate, returned only to their baseline intake and did not regain the weight that they had lost. Older people also have a reduced ability to detect and respond to dehydration. The combination of age-related physiological anorexia and impaired homeostasis means that both older people and young adults do not respond to acute undernutrition. Consequently, after an anorectic insult (for example, major surgery), older people are likely to take longer than young adults to regain the weight lost, remain undernourished longer and be more susceptible to subsequent superimposed illnesses, such as infections.

Pathological anorexia and undernutrition in older people

Protein-energy malnutrition is particularly likely to develop in the presence of other 'pathological' factors, many of which become more common with increased age (Table 16.2). The majority are at least partly responsive to treatment, so recognition is important.

Poverty

One of the social factors that contributes to decreased food intake in the elderly is poverty, which is associated with an increased rate of hunger and food insecurity.[23] Many older individuals have limited financial means, which makes it difficult to afford food of good nutritional quality.

Social isolation

Older people are more likely to live alone than young adults. Social isolation and loneliness have been associated with decreased appetite and energy intake in the elderly.[24] Elderly people tend to consume substantially more food (up to 50%) during a meal when eating in the company of friends than when eating alone. The simple measure of having older people eat in company rather than alone may be effective in increasing their energy intake.

Depression

Depression, often associated with bereavement and the deterioration of social networks, is a common psychological problem in older people, present in 2–10% of community-dwelling older people and a much greater proportion of those in institutions.[25] Depression is more likely to manifest as reduced appetite and weight loss in the elderly than in younger adults and is an important cause of weight loss and undernutrition in this group. Undernutrition *per se*, particularly if it produces folate deficiency, may further worsen depression, thus setting up a vicious cycle. Treatment of depression is effective in producing weight gain and improving other nutritional indices.[26]

Table 16.2 Non-physiological causes of anorexia in older persons.

Social factors
Poverty
Inability to shop
Inability to prepare and cook meals
Inability to feed oneself
Living alone/social isolation/lack of social support network
Failure to cater to ethnic food preferences in institutionalized individuals
Psychological factors
Depression
Dementia/Alzheimer's disease
Alcoholism
Bereavement
Cholesterol phobia
Medical factors
Cardiac failure
Chronic obstructive pulmonary disease
Infection
Cancer
Alcoholism
Dysphagia
Rheumatoid arthritis
Malabsorption syndromes
Gastrointestinal symptoms
Dyspepsia
Helicobacter pylori infection/atrophic gastritis
Vomiting/diarrhoea/constipation
Parkinson's disease
Hypermetabolism (e.g. hyperthyroidism)
Medications
Anti-infectives
Antineoplastics
Antirheumatics
Nutritional supplements
Pulmonary agents
Cardiovascular agents
Central nervous system agents
Gastrointestinal agents

Dementia

Dementia may also contribute to reduced food intake in the elderly, because individuals simply forget to eat. Up to 50% of institutionalized dementia patients have been reported to suffer from protein-energy malnutrition.[27]

Physical factors

Many older people no longer have their own teeth. Poor dentition and ill-fitting dentures may limit the type and quantity of food eaten in older persons. For example, in one study, half of 260 nursing home patients, aged 60–101 years, in Boston, USA, complained of problems with chewing, biting and swallowing. The patients with dentures were more likely to have poor protein intake than those with their own teeth.[28] Immobility (e.g. stroke), tremor

(e.g. Parkinson's disease) and impaired vision may also affect the capacity of an older person to shop for, prepare and consume food. Common medical conditions in the elderly, such as gastrointestinal disease, malabsorption syndromes, acute and chronic infection and hypermetabolism (i.e. hyperthyroidism), often cause anorexia, micronutrient deficiencies and increased energy requirements.[15] Cancer and rheumatoid arthritis, which produce anorectic effects by releasing cytokines (see the following text), are also common in older persons.

Iatrogenic/medications

The elderly are major users of prescription medications, a number of which can cause malabsorption of nutrients, gastrointestinal symptoms and loss of appetite. For example, digoxin and some forms of chemotherapy can cause nausea, vomiting and loss of appetite. Other medications can deplete the body's mineral stores; high doses of aluminium or magnesium hydroxide antacids deplete phosphate and potassium stores that can lead to muscle weakness and anorexia, and penicillamine induces zinc depletion that can lead to the loss of taste acuity and decreased food intake. The elderly often take multiple medications that increase the risk of drug interactions that can cause anorexia.

Causes of the physiological anorexia of ageing

Declining senses of taste and smell

Taste and smell are important in making eating pleasurable. The sense of taste probably deteriorates with age, although not all studies confirm this. Age-associated changes in taste may influence food choice in the elderly. There is strong evidence that the sense of smell declines with age, particularly after age 50 years. In one study, over 60% of subjects aged 65–80 years and over 80% aged 80 years or more exhibited major reductions in their sense of smell, compared with less than 10% of those aged under 50 years.[29] The decline in the sense of smell is a cause of decreased food intake in the elderly because it makes eating food less enjoyable. It may also influence the type of food eaten; several studies have shown a strong correlation between impaired sense of smell and reduced interest in and intake of food. Consistent with this effect of ageing on the types of food eaten is the observation that ageing is associated with a less varied, more monotonous diet.

Sensory-specific satiety

Sensory-specific satiety is the normal decline in pleasantness of the taste of a particular food after it has been consumed. Sensory-specific satiety leads to a decrease in the consumption of a previously eaten food and a tendency to shift consumption to other food choices during a meal. This acts to promote the intake of a more varied, nutritionally balanced diet. Older people have a reduced capacity to develop sensory-specific satiety,[30] perhaps because of reduced senses of smell and taste. Reduced sensory-specific satiety may in turn favour the consumption of a less varied diet and the development of micronutrient deficiencies.

Hormones and neurotransmitters: a selective review (Table 16.3)

The remainder of this chapter reviews, selectively, some of the emerging information about the control of food intake and why it declines with normal ageing, with particular emphasis on endocrine factors. Recently discovered hormones with effects on feeding include leptin, ghrelin and the orexins. At the time of writing, these discoveries had not yet led to evidence-based therapies, which still largely consist of nutritional supplements. The hope is that endocrine appetite stimulants or antagonists of anorexigenic hormones may have a future therapeutic role.

Table 16.3 Some endocrine factors influencing feeding and their possible contribution to the anorexia of ageing.

	Effect of ageing
Factors that stimulate feeding	
Opioids	↓ activity; not proven in humans
Neuropeptide Y	No good evidence for role
Galanin	Circulating levels unchanged, sensitivity unknown
Orexins	No good evidence for role
Ghrelin	Circulating levels possibly ↓, sensitivity unknown
Testosterone	Stimulatory role unconfirmed (?indirect), ↓ activity with age, possible effects via leptin, ghrelin and others
Factors that inhibit feeding[a]	
CART	Possible ↑ central levels (rodents)
Cholecystokinin (CCK)	↑ circulating levels, ↑ CSF levels, ↑ sensitivity to satiating effects
GLP-1	Few data, possibly ↑ activity
Peptide YY	Few data, no evidence for role
Insulin	Effect on feeding unconfirmed, no evidence for role
Leptin	Situation complex: circulating levels increase in men (↓ testosterone) *but*? leptin resistance
Cytokines	↑ activity likely

[a]CART, cocaine–amphetamine-related transcript; GLP-1, glucagon-like peptide I.

Overview of Appetite Regulation (Figure 16.1)

Central

The central feeding system is dependent on the stimulatory effect of neurotransmitters, including the opioids, noradrenaline, neuropeptide Y (NPY), the orexins, galanin and ghrelin, and the inhibitory effect of corticotrophin-releasing factor, serotonin, cholecystokinin (CCK) and possibly insulin.

Peripheral (gastrointestinal)

The short-term peripheral satiety system is largely driven by gastrointestinal mechanisms. In the longer term, factors such as leptin and cytokines (see the following text) become more important. Gastrointestinal sensory and motor functions are important in the regulation of satiation. Sensory signals induced by the distension by food contribute to initial sensations of fullness during a meal. These sensations are mediated via vagal mechanisms from mechanoreceptors situated within the stomach wall. In young adult humans, gastric distension, using a barostat, reduces food intake by up to 30%. Distension of the distal stomach (antrum) is related to increased sensations of fullness and is likely to be more important than distension of the proximal stomach (fundus). After eating, the stomach relaxes by a process of receptive relaxation, resulting in decreased intragastric pressure and increased gastric volume. This relaxation is particularly marked in the proximal stomach and results in a proximal fundic reservoir where food is retained. Not long before it is emptied into the small intestine, food is propelled distally from the fundus into the antrum. The extent of antral filling and distension relates more closely to feelings of fullness and satiety than does proximal gastric distension. Studies in animals and humans have demonstrated a relationship between postprandial satiety and the rate of gastric emptying. Slowing of gastric emptying may reduce appetite and food intake by increasing and prolonging antral distension and by prolonging the effect of small intestinal satiety signals. People with gastroparesis often exhibit symptoms of early satiety, loss of appetite, nausea and vomiting, and studies in both animals and humans have shown that there is a relationship between postprandial satiation and the rate of gastric emptying.

Once food has entered the small intestine, mechano- and chemoreceptors relay signals to the hypothalamus, resulting in the cessation of food intake. These signals are mediated by the release of gastrointestinal peptide hormones, including CCK, peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). A number of gastrointestinal and pancreatic hormones, including CCK, GLP-1 and amylin, have feedback effects on the stomach to slow gastric emptying, an effect associated with increased fullness and reduced food intake, by increasing and prolonging gastric distension and prolonging the effect of small intestinal satiety signals. Feedback signals from peripheral fat cells via leptin and, possibly, TNF-α and also absorption of nutrients from the gut also contribute to satiation.

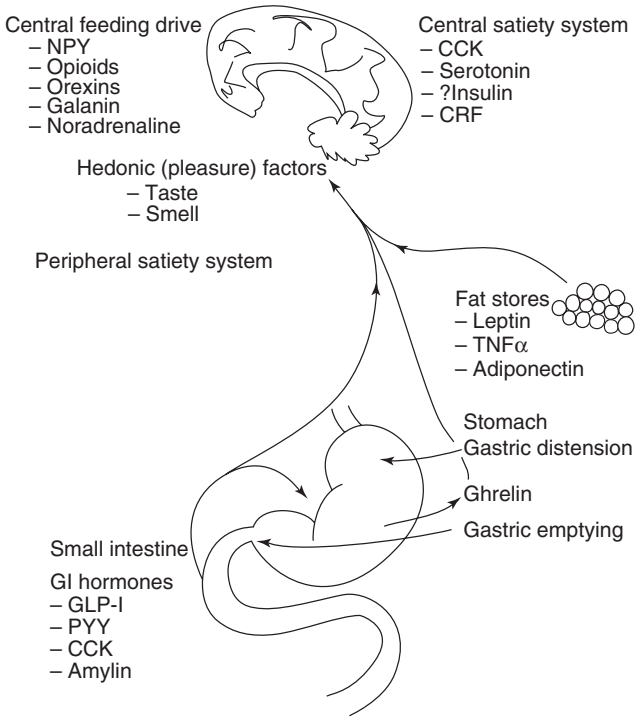

Figure 16.1 Overview of the mechanisms involved in appetite regulation.

The ageing gut

Aging is associated with cell loss in the myenteric plexus of the human oesophagus and a decline in conduction velocity within visceral neurones. The consequent reduction in sensory perception may contribute to reduced food intake by inhibiting the positive stimuli for feeding. The elderly frequently complain of increased fullness and early satiation during a meal. This may also be related to changes in gastrointestinal sensory function; ageing is associated with reduced sensitivity to gastrointestinal tract distension. If anything, reduced sensitivity to the satiating effects of distension might be expected to increase, not decrease, the food intake in older people. Nevertheless, proximal gastric distension has been found to have similar effects on food intake in healthy older and young adults and the role, if any, of impairment of gastric sensory function in causing anorexia of ageing is unknown. Ageing is probably associated with impaired receptive relaxation of the gastric fundus. As a result, for any given gastric volume, there is more rapid antral filling and distension and earlier satiety. This impaired gastric accommodation response in the elderly may be because of altered fundic nitric oxide

(NO) concentrations. Peripheral NO causes receptive and adaptive relaxation of the stomach, leading to dilation of the fundus and, ultimately, slower gastric emptying. The increase in NO with ageing may therefore contribute to the slower gastric emptying observed in the elderly. Most, but not all, studies indicate that gastric emptying slows slightly, but significantly, with increasing age. Clarkston *et al*.[18] found that healthy older subjects were less hungry and more satiated after a meal than young subjects and that postprandial hunger was inversely related to the rate of gastric emptying. The effects of ageing on gastric emptying rate may require ingestion of a relatively large energy content, as small meals have not been shown to have different emptying rates in old compared with young individuals. Delayed gastric emptying in older people may result, in part, from enhanced release of small intestinal hormones such as CCK (see the following text). In contrast, it seems that age has little, if any, effect on small intestinal or colonic motor function and orocaecal and whole gut transit time are not affected in the healthy elderly. Healthy older people do have slower phase III migration velocities and more frequent 'propagated contractions' in the small intestine, but no differences in duration of postprandial motility or amplitude or frequency of either fasting or postprandial pressure waves.

Central neurotransmitters and hormones

Monoamines

The central aminergic system has effects on feeding, with noradrenaline having stimulating, serotonin having inhibiting and dopamine having region-specific stimulatory or inhibitory effects. Ageing may be associated with increased satiating effects of serotonin, without apparent effects on dopamine or noradrenaline.

Opioids

Endogenous opioids play a role in mediating the short-term sensory reward response to food. Exogenous administration of opioid agonists increases food intake in animals and opioid antagonists decrease food intake in animals and adult humans.[31] There is evidence that ageing is associated with a reduced opioid feeding drive (reviewed by Horwitz *et al*.[32]). Elderly patients with idiopathic, senile anorexia have lower plasma and CSF β-endorphin concentrations than normal-weight, age-matched controls.[33] Intraperitoneal (i.p.) morphine injection increases food intake in young but not old mice, whereas i.p. naloxone decreases food intake in young but not older rats. Healthy older men are less sensitive to the inhibitory effects of subcutaneous naloxone on fluid intake than young men[34] and, in one small study of feeding in humans, the suppression of food intake by naloxone was non-significantly greater in the older than young adults: 16 versus 8%.[31] Overall, these results suggest that the stimulatory effect of endogenous opioids does decline somewhat with advancing age and may contribute to the anorexia of ageing. Further work is required to clarify these changes.

Neuropeptide Y

NPY is synthesized in the peripheral nervous system and brain and strongly stimulates food intake. There is preliminary evidence from animal studies that ageing may be associated with reduced NPY activity, perhaps more in males than females. Old rats have lower levels of arcuate nucleus prepro-NPY mRNA than young rats and hypothalamic NPY levels decrease with ageing in male but not female rats. Studies in humans, however, suggest, if anything, *increased* NPY activity with increasing age. CSF NPY levels increase with healthy ageing in women and plasma and CSF levels are increased in elderly people with idiopathic anorexia.[33] In rats, the feeding response to hypothalamic NPY injections diminishes with ageing, whereas the stimulation of feeding by intracerebroventricular NPY administration in mice does not diminish with age. The effects of NPY administration in humans have not been reported. There is currently, therefore, no convincing evidence for an involvement of NPY in the human anorexia of ageing.

Galanin

Galanin is a peptide hormone located in the brain and periphery, which stimulates food intake. Available animal evidence does not suggest a decline in galanin levels with ageing and circulating levels do not differ between young and older women.[35] Declining galanin levels are therefore unlikely to contribute to the anorexia of ageing, but reduced sensitivity to galanin might. The effect of ageing on stimulation of feeding by galanin has not been reported in humans, but older women (not men) display a reduced growth hormone secretory response to galanin compared with young adults.[36]

Orexins (hypocretins)

Orexin A and B (hypocretin-1 and -2) are neuropeptides synthesized in the hypothalamus and involved with feeding and sleep. Orexin deficiency causes narcolepsy in animals and humans and hypophagia and weight loss in animals.[37] Intracerebroventricular orexin injection dose-dependently increases food intake in rodents and orexin antibody reduces food intake (reviewed by Kirchgessner[38]). Orexin A is the subtype mainly responsible for effects on feeding. The majority of evidence does not support declining orexin activity as a cause of the anorexia of ageing. In a cross-sectional study of 82 healthy men and women aged 23–79 years, plasma orexin A concentrations increased with age in both men and women,[37] which should, if anything, favour *increased* appetite and food intake. Studies in mice

have found no changes or increases in total brain orexin levels and hypothalamic orexin A receptor levels with increasing age, while a decrease in hypothalamic orexin gene expression in ageing rats has been described.[39] In humans, the effects of normal ageing on the levels of the orexin receptors and sensitivity to the effects of orexin are unknown.

Cocaine–amphetamine-regulated transcript (CART)

CART is a peptide widely distributed in the brain, including the hypothalamus. In animals, central CART administration reduces feeding and blocks NPY-induced feeding. Sohn *et al*.[40] reported that arcuate nucleus CART mRNA levels were higher and NPY mRNA levels lower in healthy old than young, male rats, whereas testosterone treatment of castrated, older rats significantly lowered CART mRNA levels and increased NPY mRNA levels. This suggests that in males there is ageing-related increased central activity of CART and reduced activity of NPY, both mediated by the normal age-related decline in testosterone. This is an intriguing possibility, but the effects of ageing on CART in female animals have not been reported, nor have those in humans. The evidence that age-related increases in central CART levels may be a cause of the anorexia of ageing is therefore currently derived from one study in male rodents.

'Peripheral' hormones, including gut peptides

Cholecystokinin (CCK)

CCK is present in the hypothalamus, cortex and midbrain and is released from the lumen of the intestine in response to nutrients, particularly fat and protein, in the gut. CCK causes contraction of the gallbladder and relaxation of the sphincter of Oddi. Exogenous CCK administration decreases food intake in animals and humans. CCK is probably a physiological satiety hormone as its suppressive effect on food intake occurs with the administration of doses producing plasma CCK concentrations within the physiological range and administration of CCK antagonists increases food intake in animals and young adult humans.[41] CCK also slows gastric emptying. The satiating effects of CCK appear to increase with age. Most studies in humans have shown plasma CCK concentrations to be higher in healthy older than young adults.[42] Elderly people with idiopathic anorexia have significantly higher plasma levels and non-significantly higher CSF levels of CCK than healthy age-matched controls.[33] Intraperitoneal CCK suppresses food intake more in old than young rats and mice. Intravenous CCK-8 administration has been found to acutely suppress food intake twice as much (31 vs 15%, $p = 0.02$) in older than young adult healthy, human subjects.[43] The combination of increased circulating CCK concentrations and enhanced sensitivity to CCK suggests that CCK may be a cause of the anorexia of ageing and raises the possibility of using CCK antagonists to increase energy intake in undernourished older people.

Glucagon-like peptide-1 (GLP-1)

GLP-1 is released by the lining of the intestine in response to nutrient ingestion, particularly carbohydrates. It stimulates insulin secretion and, together with gastric inhibitory peptide (GIP), is one of the incretin hormones. It also slows gastric emptying. Administration of GLP-1 to humans increases feelings of fullness and reduces food intake.[44] Studies on the effects of ageing on plasma GLP-1 concentrations have found either no effect or increased levels in older people.[42] Further studies are needed to determine if increased GLP-1 activity is a cause of the anorexia of ageing.

Peptide YY (PYY)

PYY is a peptide hormone present in the brain and released from the bowels in response to the presence of fat and carbohydrate in the small intestine. PYY is involved in physiological processes such as memory, pain, blood pressure regulation, appetite and anxiety.[45] In rodents, feeding is increased by central PYY administration, but decreased by peripheral administration. Intravenous infusion of PYY to normal-weight and obese humans aged less than 50 years, in doses that produce postprandial blood levels, reduces short-term food intake by ~30%.[46] This suppression may be mediated by the associated suppression of ghrelin levels, whereas leptin, insulin and GLP-1 are unaltered. There is currently no evidence favouring alterations in PYY activity as a cause of the anorexia of ageing and no difference in plasma PYY concentrations, fasting and in response to intraduodenal nutrient infusions between young and older subjects. Because there is a strong negative correlation between fasting plasma PYY levels and BMI in healthy, non-elderly subjects, studies involving accurate body composition analysis are needed to determine the true effect of healthy ageing on PYY. The effects of ageing on sensitivity to the appetite-suppressant effects of PYY have not been reported.

Leptin

Leptin is produced predominantly in adipose tissue and circulates in amounts directly related to the size of fat stores. It suppresses appetite and food intake. Congenital leptin deficiency in humans is a very rare cause of morbid obesity associated with hyperphagia and leptin treatment produces substantial weight loss in these people. Most obese people, however, have elevated circulating leptin concentrations consistent with their increased fat mass. Leptin resistance is probably a feature of most human obesity and leptin administration to obese people has resulted in only minor weight loss. Although adipose tissue leptin mRNA expression increases with age in mice and rats,

studies in rats and pigs have not found an increase in serum leptin with ageing. Plasma leptin concentrations in humans often increase with ageing, to a large extent because of the increased fat mass that also accompanies ageing. Most studies show that adjustment for fat mass removes this effect.[47] This is certainly so in women, but in men some but not all studies have shown ageing to be associated with an increase in circulating leptin levels, even allowing for fat mass. This appears to be because of age-related decreases in circulating testosterone concentrations. After adjusting for fat mass, plasma leptin levels in men are inversely related to plasma testosterone, while testosterone therapy reduces and inhibition of testosterone production increases circulating leptin levels.[48]

Little is known about the effects of ageing on sensitivity to the effects of leptin. Circulating levels of the soluble leptin receptor do not change with age in humans. Resting energy expenditure and carbohydrate oxidation are predicted by fat-free mass and serum leptin concentration in middle-aged, premenopausal women, but the relationship between fat store size and plasma leptin is much weaker in older adults.[49] Fasting normally dramatically suppresses plasma leptin concentrations, thus stimulating hunger. Reduced suppression of leptin levels by fasting has been reported in ageing rats. Conversely, food intake, fat mass and insulin action are suppressed less by leptin administration in older than young rats. This suggests that ageing may be accompanied by leptin resistance, which would tend to *increase* food intake. The impact of human ageing on the effects of fasting on leptin levels and of leptin administration has not been reported.

Ghrelin

Ghrelin stimulates feeding and growth hormone release. It is present in the hypothalamus but the main site of production is the gastric mucosa. Circulating ghrelin concentrations increase with fasting and with diet-induced weight loss in obese subjects and are elevated in underweight, undernourished young and older subjects. In contrast, circulating concentrations decrease after ingestion of food, particularly fat and carbohydrate, and are reduced in obese people. These changes are consistent with compensatory responses to, rather than causes of, these altered nutritional states. It therefore seems unlikely that reduced ghrelin activity contributes significantly to the anorexia and weight loss in markedly undernourished older subjects. Nevertheless, the effects of ageing and undernutrition on sensitivity to ghrelin have not been reported and ghrelin resistance may occur in these states. In support of this, older subjects are less sensitive to the growth hormone (GH)-releasing effects of intravenous ghrelin (i.v. ghrelin) than young adults.[50] The effect of healthy ageing on circulating ghrelin concentrations has not yet been clarified. A possible rationale for a decline in ghrelin levels with age, particularly in men, is the positive association between circulating testosterone and ghrelin concentrations and the increase in plasma ghrelin concentrations that occurs in hypogonadal men in response to testosterone therapy.[51] As normal ageing is accompanied by reductions in circulating androgen levels (see the following text), this might have the effect of reducing ghrelin concentrations and thus food intake. One study found a rise in plasma ghrelin concentrations with increasing age, but there was no relationship with age *per se* when a multivariate analysis was performed[52] and the study did not include subjects older than 64 years. Two small studies have reported circulating ghrelin concentrations 20%[53] and 35%[54] lower in healthy older (69–87 and 67–91 years, respectively) than young adults, the latter reduction being statistically significant. However, increasing body fat, as indicated by BMI, is associated with decreasing ghrelin concentrations and the older subjects had higher BMIs than the young subjects in both studies. Neither study included detailed body composition analysis, so the lower ghrelin levels in older subjects may have been because of differences in body composition. Another study found no difference in fasting and postprandial serum ghrelin concentrations between healthy older (mean age 78 years) and young adults.[55] On balance, the effect of healthy ageing on circulating ghrelin concentrations has not yet been clarified, but is probably minimal.

Insulin

Human ageing tends to be associated with increased fasting and postprandial circulating insulin concentrations.[56] Increased insulin activity could, therefore, be a cause of reduced food intake in older people. The evidence for a satiating role of insulin is, however, limited. Suppression of food intake by insulin has only been demonstrated in animals and has required central insulin administration at high doses or high-dose, prolonged peripheral administration. Short-term, peripheral, euglycaemic insulin infusions have been shown not to affect appetite or food intake in humans.[57] Moreover, age-associated increases in insulin concentrations are due mainly to insulin resistance resulting from increased adiposity and only to a small extent to ageing itself. It seems unlikely that insulin contributes substantially, if at all, to the anorexia of ageing.

Testosterone and other androgens

Circulating androgen concentrations decline with ageing. This may contribute to the development of sarcopenia and the decrease in functional status that occurs with ageing (reviewed by Bhasin[58]). Whereas androgen replacement therapy (ART) is advocated for men with marked androgen deficiency, there is no consensus for the use of ART in elderly men with less severe ageing-related declines in androgen concentrations or in elderly women.

Studies of androgen replacement have been performed in healthy, older men with androgen deficiency, but although benefits have been seen in muscle mass and, in some cases, strength, there is, as yet, no agreement that this leads to improvements in functional status (reviewed by Morley[59]). Several recent studies have suggested that there may be benefits from treating older men, particularly if frail, with testosterone therapy. Amory *et al*.[60] gave older men with a mean total testosterone within the normal range 600 mg i.m. testosterone weekly for 4 weeks before elective knee replacement surgery and found significant increases in the ability to stand postoperatively and trends to improvements in walking and stair climbing, compared with placebo-treated men. Bakhshi *et al*.[61] gave older men in a rehabilitation programme with low-normal testosterone levels 100 mg i.m. testosterone or placebo weekly and found significant increases in grip strength and the Function Independence Measure after testosterone but not placebo. Chapman *et al*.[62] showed a reduced rate of hospitalization over 1 year in older men and women either undernourished or at risk of undernutrition given a combination of oral testosterone and a nutritional supplement compared with an untreated group. Srinivas-Shankar *et al*.[63] treated older, frail men with low circulating testosterone concentrations with transdermal testosterone or placebo for 6 months and found improvements in muscle strength and also physical function, the latter effects confined to older (≥75 years) and more frail men. These results are not conclusive but justify further studies of testosterone treatment in frail, older people.

In women, serum concentrations of testosterone and the adrenal androgens gradually and progressively decline from the decade preceding menopause. Even if testosterone therapy does not increase food intake in older, undernourished people, it may provide functional benefits by treating the associated sarcopenia and studies to examine this are under way.

Cytokines

Age-associated increases in the production and/or effect of satiating cytokines may contribute to the anorexia of ageing.[64] Cytokines are secreted in response to significant stress, often because of malignancy or infection. Circulating concentrations of the cytokines interleukin 1 (IL-1), interleukin 6 (IL-6) and TNF-α are increased in cachectic patients with cancer or AIDS. They act to decrease food intake and reduce body weight via a number of central and peripheral pathways. Blockade of these cytokines, for example, of TNF-α in mice with TNF-producing sarcomas, significantly attenuates weight loss in high-stress conditions associated with cachexia. Ageing itself may be a form of stress. It is associated with stress-like changes in circulating hormonal patterns; increased cortisol and catecholamines and decreased sex hormones and growth hormone. Increased cortisol and catecholamine levels, in turn, stimulate the release of IL-6 and TNF-α, whereas sex hormones inhibit IL-6. Interleukin 1 and IL-6 levels are elevated in older people with cachexia, whereas plasma IL-6 concentrations apparently increase as a function of normal ageing and correlate inversely with levels of functional ability in elderly people. Higher circulating levels of CRP and cytokine receptors appear also to be associated independently with physical dysfunction and disability.[65] Increased cytokine levels, due to the 'stress' of ageing *per se* or the amplified stressful effects of other pathologies, may thus provide an explanation for some of the decline in appetite and body weight that occurs in many older people.

Diagnoses and treatment of undernutrition in older people

These are covered in Chapter 15, Epidemiology of nutrition and ageing, and Chapter 17, Weight loss.

Key points

- On average, food intake is about 30% lower in the elderly than young adults, because of a physiological decrease in appetite, the anorexia of ageing. This predisposes to the development of protein-energy malnutrition, which is surprisingly common in the elderly.
- The physiological anorexia of ageing predisposes to the development of pathological anorexia and undernutrition when factors that become more common with ageing, such as depression, dementia, poor dentition, social isolation, medications and various illnesses, are superimposed.
- A number of hormones involved in the control of feeding have been discovered recently and knowledge of the hormonal control of feeding is expanding rapidly. Understanding of the anorexia of ageing is in its infancy.
- Current evidence supports the following as causes of the anorexia of ageing:
  ↑ activity CCK
  ↑ activity cytokines
  ↓ activity androgens (particularly in men)
  weaker evidence for ↓ activity ghrelin, ↑ leptin.

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CHAPTER 17

Weight loss

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Introduction

Weight loss is common in older adults and is a harbinger of poor outcome. A loss of 10% or more of body weight between age 50 years and old age is associated with a 60% increase in mortality compared with persons with stable weight.[1] Involuntary weight loss greater than 4% of body weight is an independent predictor of increased mortality in older community-dwelling male veterans. Over a two-year follow-up period, mortality rates were substantially higher in the 13% of the population with involuntary weight loss (28%) than in those who did not lose weight (11%), even after adjusting for baseline age, body mass index, tobacco use and other health status and laboratory measures.[2]

Weight loss is strongly associated with a 76% increase in mortality risk among home-bound older adults, along with male gender and age. This effect of weight loss persists after adjusting for initial body mass index (BMI) (the weight in kilograms divided by the height in metres squared), smoking, health status and functional status.[3]

In nursing home residents, a 10% loss of body weight over a six-month interval strongly predicted mortality in the ensuing six months.[4] When compared with controls, the 16% of subjects who lost at least 5% of their body weight were 4.6 times more likely to die within 1 year.[5] In another study of long-term care residents, a 10-fold increased risk for death was seen for persons who lost 5% of their body weight in any month compared with those who gained weight.[6] For this reason, the United States Long-Term Care Minimum Data Set defines a loss of greater than 10% of body weight within 180 days or 5% within 30 days as an important clinical threshold for triggering resident assessment protocols.[7]

Weight loss is also associated with a decline in functional status. Weight loss of more than 5% in community-dwelling women 60–74 years old was associated with a twofold increase in risk of disability over time, compared with women who did not lose weight, after adjustments for age, smoking, education, study duration and health conditions.[8] Weight loss and undernutrition are also related to functional decline in nursing home residents.[9]

Body weight and weight adjusted for height (BMI) are easily obtained clinical measurements that can predict adverse outcomes in older persons.

The relationship of weight loss to mortality

A body mass index of less than 22 $kg\,m^{-2}$ has been associated with a higher one-year mortality rate and with poorer functional status among older community-dwelling persons.[10] The risk for higher mortality in men older than 65 years begins at a BMI of less than 22 $kg\,m^{-2}$ and increases to a 20% higher risk in men older than 75 years with a BMI of less than 20.5 $kg\,m^{-2}$. Similarly, a higher mortality risk in women begins at a BMI of less than 22 $kg\,m^{-2}$ in women older than 65 years and increases to a 40% higher risk in women older than 75 years with a BMI of less than 18.5 $kg\,m^{-2}$.[11] BMI less than the 15th percentile is an independent predictor of 180 day mortality following hospitalization.[12]

Although there is a strong association between BMI and mortality, the key factor in mortality risk appears to be recent weight loss. Recent weight loss, rather than current BMI, is the strongest predictor for mortality. After excluding subjects with weight loss of 10% or more of their body weight, there is little relationship between BMI and mortality.[13] In persons over 50 years of age who reported an unintended loss of 10 lb (~3.7 kg) or more in the year before evaluation, the age-adjusted death rate was much higher compared with persons who voluntarily lost weight through diet or exercise or who maintained or gained weight.[14] Nearly all of the observational studies on body weight have found that any weight loss is associated with increased, rather than decreased, risk for death.

The data suggest that obesity in older adults may not be an important clinical target for reducing mortality and

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that a preferred public health emphasis for this age group would be to increase awareness that substantial weight loss after age 50 years is a potential indicator for poor prognosis.

Body weight in the general population is not stable. Some 29% of men and 44% of women in the USA report that they are attempting to lose weight, and 35% of men and 34% of women report that they are attempting to maintain weight. The most common strategy among those attempting to lose weight was to consume less fat, but not fewer calories (35% of men and 40% of women). Only 22% of men and 19% of women reported using a combination of eating fewer calories and engaging in at least 150 min of leisure-time physical activity per week.[15]

In an observational study, overweight and obese persons who were at least 35 years of age and who had a BMI greater than 25 kg m^{-2}, self-reported their intention to lose weight and then reported actual weight change during the past year. Those persons reporting an intentional weight loss had a 24% lower mortality rate compared with persons not trying to lose weight and reporting no weight change. However, mortality rates were independent of actual weight change. The persons who reported trying to lose weight but who had no weight change also experienced a 20% reduction in mortality risk. An unexpected finding was that a decreased mortality rate was also found among those who reported gaining weight but who were not trying to lose weight. In this study, an attempt at weight loss was associated with lower all-cause mortality, but was independent of weight change. A higher mortality rate (31%) occurred only in those persons reporting unintentional weight loss.

Paradoxically, a higher two-year mortality was found in community-living subjects who lost weight by dieting (36%) compared with those who had involuntary weight loss (28%). These data suggest that even voluntary weight loss by dieting may place older persons at risk. The recommendation that older adults voluntarily reduce body weight cannot be supported by the literature and may be hazardous.

Effect of weight loss on comorbid conditions

Only limited data support the notion that intentional weight loss reduces total mortality. However, mortality is only a small part of the substantial burden of disease caused by obesity-related conditions such as hypertension, diabetes mellitus, coronary artery disease, degenerative arthritis and cancers of the breast, uterus and colon. Short-term reductions in caloric intake (dieting) have favourable effects on blood pressure, cholesterol and metabolic rate. These benefits require at least a 20% reduction in caloric intake.

Weight loss has been shown to reduce disease-specific risks such as hypertension and type 2 diabetes. However, it should be noted that overweight/obesity-related comorbidities, particularly those associated with the insulin resistance syndrome (e.g. hypertension, dyslipidaemias and hyperinsulinaemia) can be improved independently of weight loss.[16,17] Blood pressure can be lowered in the absence of weight loss by dietary changes.[18] The effect on blood pressure by non-pharmacological interventions can be maintained for 3–5 years despite significant increases in body weight.[19] Other trials of coronary artery disease have shown prevention effects to be independent of weight loss. The data suggest that improvements in comorbid conditions can be enhanced with lifestyle changes, but that the effect is independent of whether weight loss occurs.

Causes of weight loss

The regulation of body composition is dynamic over time. Minute-to-minute composition is regulated by a person's metabolic state. Day-to-day regulation depends of insulin and glucagon. Month-to-month, hormones such as estrogens and androgens, growth hormone, prolactin, thyroid hormones, catecholamines and corticosteroids regulate body composition. Immune mediators, such as interleukin-1, tumour necrosis factor and interleukin-2, also can affect body composition through modulation of appetite and food intake and direct effects on skeletal muscle.[20]

Weight loss can be either voluntary (a conscious decision to reduce body weight by either restricting calories or increasing energy expenditure) or involuntary (absence of any intention to reduce weight). Involuntary weight loss can occur from a variety of causes, including ingestion of inadequate calories (starvation), disuse atrophy or hormonal deficiencies (sarcopenia), a decrease in appetite (anorexia) or the effects of disease (cachexia), and a combination of these factors[21] (Table 17.1).

Starvation

Simple starvation is caused by pure protein–energy deficiency. Starvation can be short-term (fasting) or long-term (chronic protein–energy undernutrition). Worldwide, starvation is most often caused by lack of food. In developed countries, starvation is usually associated with disease. Starvation occurring in the presence of adequate food results from inability to swallow, a non-functioning gastrointestinal tract or failure of appetite (anorexia).

Older persons ingest fewer calories than younger adults. On average, persons over the age of 70 years consume one-third less calories compared with younger persons.[22] About 16–18% of community-dwelling elderly persons consume less than 1000 kcal daily.[23] This reduction in intake places older adults at risk for protein–energy, vitamin and mineral undernutrition.

Table 17.1 Causes of weight loss.

Type	Mechanism	Cause
Intentional	Decreased caloric intake	Voluntary restriction
	Increased energy expenditure	Exercise
Unintended	Anorexia	Impaired appetite
	Starvation	Inadequate access to food
		Inability to swallow food
		Inability to absorb food
	Cachexia	Cytokine-mediated disease
	Sarcopenia	Age-related loss of muscle mass

The decline in energy intakes that accompanies ageing has been the subject of intensive investigation. Total energy expenditure (TEE) declines with ageing, chiefly due to changes in resting energy expenditure (REE). REE decreases by 10–20% with age, primarily due to a decrease in muscle mass.[24,25] REE is higher in active older adults than sedentary older adults,[26] but a decline in muscle mass occurs in both sedentary and active ageing adults.[27] A decrease in physical activity largely explains the decline in TEE with age.[28] Surprisingly, there is little correlation between physical activity and fat mass in older persons. Higher physical activity is not associated with a lower body fat mass in subjects older than 60 years.

Sarcopenia

Unintended weight loss in older persons may result from a decrease in fat-free mass. Sarcopenia is operationally defined as an appendicular skeletal muscle mass divided by height in metres of more than two standard deviations below the young normal mean. Using this definition, Baumgartner *et al*. found that 14, 20, 27 and 53% of men aged less than 70, 70–74, 75–80 and over 80 years, respectively, met this definition. In women, 25, 33, 36 and 43% in the same age groups had sarcopenia.[29] Although a decrease in muscle mass is the hallmark of sarcopenia, not all sarcopenic persons have a low body mass. At a BMI cut point of $\sim 27\ kg\ m^{-2}$, 14% of men less than 70 years old and 29% of men more than 80 years old were sarcopenic and obese and 5% of women less than 70 years old and 8% of women more than 80 years old were sarcopenic and obese. Although the decline in muscle mass should be reflected in body weight, an increase in fat mass may obscure the body weight loss. Therefore, a relatively small proportion of sarcopenic persons do not exhibit a decrease in body weight.

The fact that muscle mass decreases with age has been known for some time. Earlier work demonstrated that the excretion of urinary creatinine, a measure of muscle creatine content and total muscle mass, decreases by nearly 50% between the ages of 20 and 90 years. This age-related loss of muscle mass appears to be fairly consistent, at a rate of ~1–2% per year after the age of 50 years, and occurs in both sedentary and active ageing adults. In contrast, in healthy young adults, no net change occurs in skeletal muscle mass under equilibrium conditions due to the balance in skeletal muscle protein synthesis and degradation. This age-related reduction in muscle mass and strength is also accompanied by a reduction in motor unit number[30] and by atrophy of muscle fibres, especially the type IIa fibres.[31] An associated decline in protein synthesis, particularly in the synthesis of myosin heavy chains, has been observed.[32]

The loss of muscle mass with ageing is clinically important because it leads to diminished strength and exercise capacity.[33] Dynamic, static and isokinetic muscle strength decreases with age.[34] Maximum oxygen consumption declines with age[35] at a rate of 3–8% per decade beginning at age 30 years. However, after correction for muscle mass, there is no important decline in $VO_{2\,max}$ with ageing, indicating that a change in muscle mass is the significant factor.[36] Up to 65% of older men and women report that they cannot lift 10 lb (~3.7 kg) using their arms.[37] Although sarcopenia is due to a reduction in skeletal muscle mass, not all subjects demonstrate a loss in body weight. An increase in fat mass accompanying ageing may mask the loss of non-fat mass, resulting in normal or even an obese body weight in sarcopenic persons.

Cachexia

Cachexia is the cytokine-associated wasting of protein and energy stores due to the effects of disease. Systemic inflammation mediated through cell injury or activation of the immune system triggers an acute inflammatory response. Persons with cachexia lose roughly equal amounts of fat and fat-free mass while maintaining extracellular water and intracellular potassium. The loss of fat-free mass is mainly from the skeletal muscle.

Table 17.2 Conditions associated with cachexia.

Infections, e.g. tuberculosis, AIDS
Cancer
Rheumatoid arthritis
Congestive cardiomyopathy
End-stage renal disease
Chronic obstructive pulmonary disease
Cystic fibrosis
Crohn's disease
Alcoholic liver disease
Elderly persons without obvious cause

Cytokines are related to a number of disease conditions, including cancer, end-stage renal disease, chronic pulmonary disease, congestive heart failure, rheumatoid arthritis and AIDS[38] (Table 17.2). In subjects with pneumonia, the admission concentrations of α_1-antitrypsin and α_1-acid glycoprotein are better predictors of hospital morbidity than albumin and C-reactive protein levels.[39] In subjects with end-stage renal disease on haemodialysis followed for 3 years, increased IL-1, TNF-α, IL-6 and IL-13 levels were significantly associated with increased relative mortality risk, whereas higher levels of IL-2, IL-4, IL-5, IL-12, T-cell number and function and CH50 were associated with improved survival.[40] Although the cancer anorexia–cachexia syndrome is present in 50% of advanced cancer patients and in 80% of terminally ill cancer patients, serum levels of cytokines are not always directly associated with the onset of cancer anorexia–cachexia syndrome.[41]

Cytokines have a direct negative effect on muscle mass and increased concentrations of inflammatory markers have been associated with a reduced lean mass.[42–44] This direct effect also has been associated with a decline in muscle strength in older adults.

Increasingly, a consensus on the differential effects of starvation and cachexia is developing.[45] Starvation can frequently be distinguished from cachexia (Table 17.3). However, in later stages this distinction is more difficult. The hallmark of starvation is a rapid response to refeeding.

Anorexia

A direct effect of systemic inflammation is appetite suppression. Cytokines directly result in feeding suppression and a lower intake of nutrients and cachexia is nearly always accompanied by anorexia. IL−1β and TNF-α act on the glucose-sensitive neurons in the ventromedial hypothalamic nucleus (a 'satiety' site) and the lateral hypothalamic area (a 'hunger' site).[46]

Acute illness is characterized by a spontaneous decrease in food intake despite an increased need for energy and nutrients.[47] Although seemingly paradoxical, the voluntary suppression of food intake during illness is common to most species. The relationship between hedonic qualities of food, gastrointestinal and central satiation drives and hormonal relationships may explain this observed difference.[48] This response is the most common cause of anorexia observed in the acute care setting.[49] The data suggest that cytokine levels are commonly associated with disease conditions characterized by cachexia and may play a role in mortality, weight loss and appetite suppression. In contrast to starvation, cachexia is remarkably resistant to hypercaloric feeding.

Anorexia may also result from changes in the physiological regulation of appetite and satiety, as a physiological response to ageing.[50] The importance of understanding this relationship lies in addressing pharmacological[51] or dietary interventions[52] that may reverse this anorexia of ageing.

Evaluation of weight loss

Involuntary weight loss is often attributed to occult disease, but rarely is this found to be the cause. A physical cause of weight loss was clinically evident on the initial evaluation in 93% of patients. In another study, the primary cause of undernutrition was found to be identifiable in nearly 90% of medical outpatients.

The evaluation of unintended weight loss begins with identification of persons at risk. Several assessment instruments have proven validity in the assessment of weight loss or subsequent mortality. The Simplified Nutritional Appetite Questionnaire (SNAQ), a four-question assessment instrument, reliably predicts anorexia and the risk of weight loss in the next six months (Figure 17.1).

The Mini Nutritional Assessment (MNA) was developed to assess malnutrition in elderly populations (Figure 17.2).

Table 17.3 Distinguishing starvation from cachexia.

	Starvation	Cachexia
Appetite	Suppressed in late phase	Suppressed in early phase
Body mass index	Not predictive of mortality	Predictive of mortality
Serum albumin	Low in late phase	Low in early phase
Transthyretin	Low in late phase	Low in early phase
Transferrin	Low	Low
Retinol-binding protein	Low	Low
Cholesterol	May remain normal	Low
Total lymphocyte count	Low, responds to refeeding	Low, unresponsive to refeeding
C-reactive protein	Few data	Elevated
Inflammatory disease	Usually not present	Present
Response to refeeding	Reversible	Resistant

Reproduced from Thomas.[38]

Name: _____ Sex (circle): Male/Female
Age: _____Weight: _____ Height: _____
Date: _____

Administration Instructions: Ask the subject to complete the questionnaire by circling the correct answers and then tally the results based upon the following numerical scale: a = 1, b = 2, c = 3, d = 4, e = 5. The sum of the scores for the individual items constitutes the SNAQ score. SNAQ score >14 indicates significant risk of at least 5% weight loss within six months.

1. My appetite is

a. very poor
b. poor
c. average
d. good
e. very good

2. When I eat

a. I feel full after eating only a few mouthfuls
b. I feel full after eating about a third of a meal
c. I feel full after eating over half a meal
d. I feel full after eating most of the meal
e. I hardly ever feel full

3. Food tastes

a. very bad
b. bad
c. average
d. good
e. very good

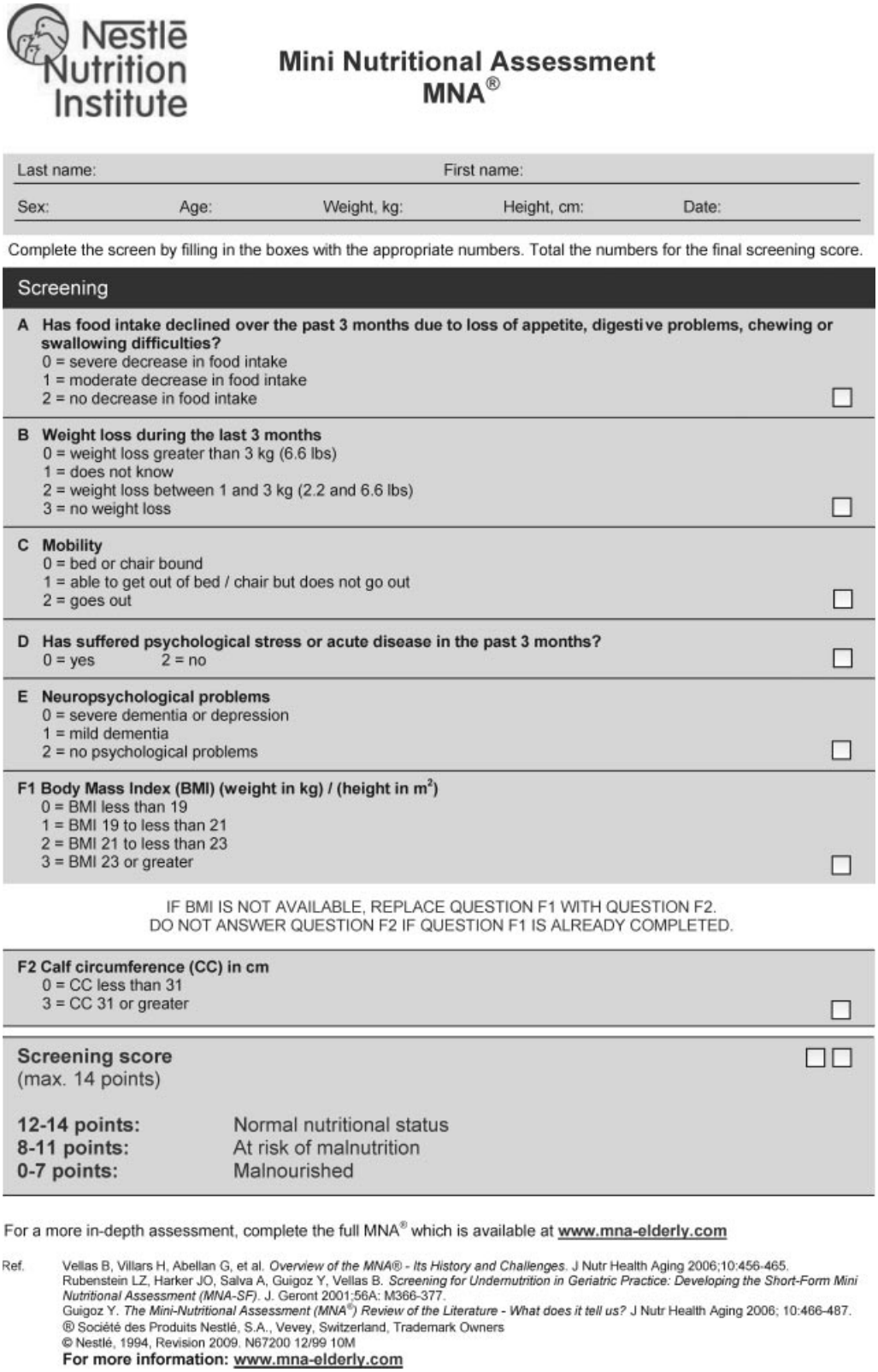
4. Normally I eat

a. less than one meal a day
b. one meal a day
c. two meals a day
d. three meals a day
e. more than three meals a day

Figure 17.1 Simplified Nutritional Appetite Questionnaire (SNAQ). Reproduced with permission from Wilson MM *et al*. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *American Journal of Clinical Nutrition* 2005;**82**(5):1074–81. Copyright © 2005, The American Journal of Clinical Nutrition.

Subjects with a normal baseline score had a lower mortality risk [0.35; 95% CI, 0.18–0.66] than subjects with an abnormal MNA score. The subjects judged to be at risk for undernutrition by the MNA had more frequent acute illness, need for more assistance and more weight loss. The MNA was found to be 96% sensitive and 60% specific for body weight loss. A subsequent analysis found that a six-item version of the MNA has equivalent predictive value.

The treatment of undernutrition in the elderly begins with a careful differential diagnostic approach aimed at finding reversible medical causes. Medical conditions that may be associated with anorexia, decreased food intake or increased metabolic requirements should be assessed. Anorexia may be associated with illness, drugs, dementia or mood disorders. Decreased food intake may result from dysphagia, chewing problems, nausea, vomiting, diarrhoea, pain or faecal impaction. Increased metabolic requirements may be precipitated by fever, infection or the presence of chronic skin wounds. Treatment of these conditions may restore appetite and body weight. An algorithm for the approach to the differential diagnosis and management of involuntary weight loss has been published by the Council for Nutrition in Long-term Care.[53]



Nestlé Nutrition Institute

Mini Nutritional Assessment MNA®

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers. Total the numbers for the final screening score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3 kg (6.6 lbs)
1 = does not know
2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F1 Body Mass Index (BMI) (weight in kg) / (height in m^2)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2.
DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.

F2 Calf circumference (CC) in cm
0 = CC less than 31
3 = CC 31 or greater ☐

Screening score (max. 14 points) ☐☐

12-14 points: Normal nutritional status
8-11 points: At risk of malnutrition
0-7 points: Malnourished

For a more in-depth assessment, complete the full MNA® which is available at **www.mna-elderly.com**

Ref. Vellas B, Villars H, Abellan G, et al. *Overview of the MNA® - Its History and Challenges*. J Nutr Health Aging 2006;10:456-465.
Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. *Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini Nutritional Assessment (MNA-SF)*. J. Geront 2001;56A: M366-377.
Guigoz Y. *The Mini-Nutritional Assessment (MNA®) Review of the Literature - What does it tell us?* J Nutr Health Aging 2006; 10:466-487.

For more information: www.mna-elderly.com

Figure 17.2 Mini Nutritional Assessment (MNA). Source: MNA® Mini Nutritional Assessment – Nestlé Nutrition Institute. Available at www.mna-elderly.com.

Table 17.4 Nutritional interventions.

Voluntarily increase intake
Oral hypercaloric supplements
Pharmacological orexigenic drugs
Anabolic steroids
Enteral feeding tube
Peripheral parenteral supplementation
Total parenteral nutrition

Interventions

For starvation

The first response of caregivers to weight loss, whether due to starvation or to cachexia, is to increase nutrient intake (Table 17.4). In a meta-analysis of 42 trials, nutritional supplementation produced a mean difference in weight gain of 2.3%. A reduced mortality was observed in the supplemented compared with control groups [relative risk (RR) = 0.74; 95% CI, 0.59–0.92] in 32 trials. The subgroup analyses suggested that the effects on mortality were consistently significant when limited to trials in which participants were defined as undernourished (RR = 0.72; 95% CI, 0.55–0.94), when 400 kcal or more was offered per day in the supplement (RR = 0.71; 95% CI, 0.56–0.90), when participants were at least 75 years old (RR = 0.69; 95% CI, 0.54–0.87), when supplementation was continued for 35 days or more (RR = 0.75; 95% CI, 0.56–1.00), when participants were unwell (RR = 0.73; 95% CI, 0.59–0.92) and when participants were in hospital or in a nursing home (RR = 0.67; 95% CI, 0.52–0.86). However, there was no evidence of improvement in functional status or reduction in length of hospital stay with supplements.[54]

A failure to consume adequate nutrients or supplements often leads to enteral feeding. Enteral feeding can frequently be life-saving, but improving nutritional parameters is difficult to verify.[55] There is little evidence for benefit in survival or comfort for enterally fed patients with weight loss due to cancer cachexia, and there are substantial associated risks, discomforts and costs.[56] Enteral feeding in nursing home residents older than 65 years with severe cognitive impairment did not affect survival at 24 months in residents fed by feeding tube compared with residents who were not enterally fed.[57] Survival in other medical conditions does not appear to be affected by enteral feeding. A downward trend in the use of parenteral nutrition in critical care patients has occurred over the last few years, chiefly due to studies showing a higher morbidity with parenteral nutrition compared with enteral nutrition.[58]

Undernourished or high-risk surgical patients did not have postoperative complications reduced to that of well-nourished patients undergoing similar procedures by enteral or parenteral support.[59] The results of percutaneous parenteral feeding in subacute patients was not optimal.[60] These data suggest that factors other than pure starvation are operational, since a response to refeeding is the hallmark of starvation.

For sarcopenia

For persons with sarcopenia, the primary intervention should include resistance exercise interventions.[46] The increase in muscle protein mass is attributable to an acute and chronic increase in muscle protein turnover, resulting in the rate of muscle protein synthesis exceeding that of muscle proteolysis. Coincident with the increase in amount of muscle protein are increases in maximum voluntary muscle strength and muscle fibre hypertrophy.[61] Progressive resistance training 2–3 times per week improves physical function and reduces physical disability and muscle weakness in older adults. Functional limitations such as balance, gait speed, timed walk, timed get up and go, chair rise and climbing stairs also improve.[62] The improvement in muscle mass and strength with resistance exercise extends even to the very old. However, little is known about the duration of these effects once training has stopped.

Bed rest reduces muscle protein synthesis and induces a loss of lean body mass, a model that simulates sarcopenia due to inactivity. Essential amino acid supplementation has been shown to stimulate muscle protein synthesis in healthy volunteers to a greater extent than meals, intact proteins or similar energy intake. Continued stimulation of muscle anabolism positively affects the preservation of lean body mass and the amelioration of functional decrement throughout inactivity. However, in the setting of critical illness, the loss of lean body mass is exacerbated by a persistent hypercortisolaemia. Although essential amino acids promote muscle anabolism during hypercortisolaemia, it is unlikely that a nutritional intervention alone would be effective in maintaining lean body mass during severe stress or prolonged hypercortisolaemia.[63]

For anorexia/cachexia

Various orexigenic stimulants to improve body weight have been studied. Corticosteroids have improved appetite, but have not demonstrated a gain in body weight in clinical trials. Cyproheptadine has been shown to increase appetite in cancer patients without weight gain. Cannabinoids (dronabinol, marinol and nabilone) have shown promise in improving mood and appetite in cancer patients and in AIDS cachexia. Thalidomide, a tumour necrosis factor inhibitor, has produced body weight gain in a small number of patients with HIV-associated wasting syndrome.

Of the pharmacological agents demonstrated to produce weight gain in patients with anorexia and cachexia,

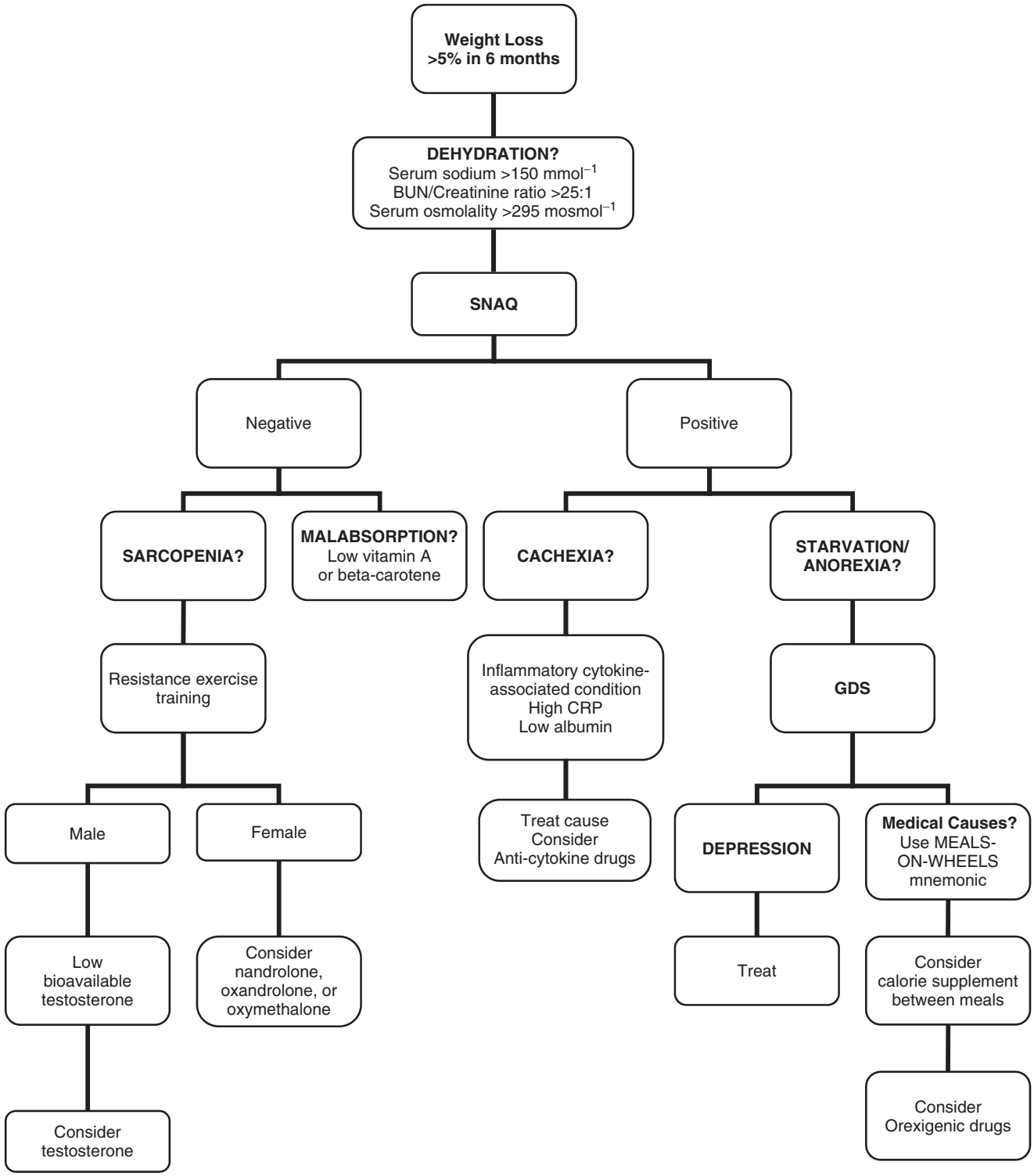


Figure 17.3 Approach to the management of weight loss. CRP, C-reactive protein; GDS, Geriatric Depression Scale; SNAQ, Simplified Nutritional Appetite Questiommaire. Reproduced from Thomas.[21] Copyright © 2007, with permission from Elsevier.

megestrol acetate has been the most widely studied agent. In a meta-analysis of 26 trials, megestrol acetate was found to increase appetite, produce weight gain and improve health-related quality of life in oncology patients, compared with placebo. In AIDS patients, increased weight was demonstrated. Only oedema was significant as an adverse event.[64]

Steroids and hormonal agents such as megesterol acetate are currently widely used in the treatment of cachexia and anorexia. They act through multiple pathways, such as increasing neuropeptide-Y levels to increase appetite and downregulating proinflammatory cytokines. Pharmacological treatment of anorexia with agents that modulate cytokine production may produce weight gain in cachexia states. The action of thalidomide has been linked to inhibition and degradation of TNF-α.[65] The results of these pharmacological trials raise the interesting hypothesis that the improvement in appetite and weight gain may be related to their effect on cytokines. Comparisons of eicosapentaenoic acid combined with a protein energy supplementation versus a protein energy supplementation without eicosapentaenoic acid in the presence of an appetite stimulant provided no evidence that eicosapentaenoic acid improves symptoms associated with the cachexia syndrome.[66]

In contrast to starvation, cachexia is remarkably resistant to hypercaloric feeding. Trials of both enteral and parenteral feeding in cancer cachexia have consistently failed to show any benefit in terms of weight gain, nutritional status, quality of life or survival.[67]

Anabolic steroids

Serum levels of both testosterone and the adrenal androgens decline with age and there are epidemiological data supporting the relationship between the fall in testosterone and the decline in muscle mass, strength and functional status.[68] Clinical trials have demonstrated that the administration of testosterone in older individuals modestly increased both muscle mass and strength, and also bone density.[69] However, while demonstrating an improvement in leg muscle strength, testosterone replacement in older hypogonadal men demonstrated a higher risk for cardiovascular events, effectively terminating the study.[70] Studies of higher doses have been limited by concern for accelerating prostate cancer.[71]

Dehydroepiandrosterone administration has shown conflicting data regarding improvement in muscle mass and strength. The results are more promising in males than in females. An anabolic–androgenic steroid, oxymetholone, produced body weight gain in advanced HIV-1 infection,[72] but not in cachectic cancer patients.[73] The weight gain usually occurred only in patients who were hypogonadal.

Administration of growth hormone in pharmacological doses increases muscle mass but not muscle strength.[74] Recombinant human growth factors have produced weight gain (mean 1.6 kg versus 0.1 kg in the placebo group) in patients with AIDS, but at substantially higher than physiological doses.[75]

Several studies suggest a potential benefit of creatine, especially when combined with exercise to increase stores of phosphocreatine in the muscle and replenish phosphocreatine and adenosine triphosphate, but more studies are needed to confirm these findings.

Conclusion

In older persons, a low BMI is associated with a higher mortality risk. When the observational studies are adjusted for weight loss, nearly all of the higher mortality risk is due to weight loss. Involuntary weight loss has an intensified effect of mortality risk and is usually associated with clinical illness. There are some data to suggest that even voluntary weight loss in older persons may carry a higher mortality risk. Body weight is an easily obtained clinical measurement and weight loss is a profound marker for adverse outcome.

A therapeutic approach to the loss of skeletal muscle mass and strength in older persons depends on correct classification. The term sarcopenia should be reserved for age-related decline in muscle mass not attributable to the presence of proinflammatory cytokines. Cachexia may be a better term for a decline in muscle mass associated with known inflammatory disease states. Although starvation due to protein energy undernutrition is widely regarded as the primary cause of loss of fat and fat-free mass in older persons, a failure to improve with nutritional replacement should trigger a consideration of other causes.

Distinguishing starvation, sarcopenia and cachexia can be difficult, since there can be an overlap between nutrient intake, hormonal deficiency and disease activation. The importance of defining the distinction lies in developing a therapeutic approach to skeletal muscle loss and muscle strength in older persons (Figure 17.3).

Key points

- Unplanned weight loss is common in older adults and is often a sign of a poor outcome.
- Weight loss may be closely associated with functional decline and the additional disability may have important consequences for dependency and place of residence.
- Effective management of weight loss requires a targeting approach to identify high risk individuals, nutritional evaluation, treatment remedial causes and use of selected nutritional supplements.

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CHAPTER 18

Dehydration

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Introduction

Water accounts for about 60% of body weight in an average human, varying mainly with degree of adiposity. As the percentage of body fat increases, the amount of body water decreases. Water is distributed in virtual compartments in the body, moving between compartments by osmosis or by pumps. Total body water (TBW) is about 42 l in a 70 kg person, or 600 ml kg^{-1}. TBW is divided into intracellular fluids (two-thirds TBW, 400 ml kg^{-1}) and extracellular fluids (one-third TBW, 200 ml kg^{-1}). About 75% of the extracellular fluid is distributed interstitially between cells (150 ml kg^{-1}) and about 25% of extracellular fluid is found in the intravascular space (50 ml kg^{-1}).[1]

The spaces define the clinical syndromes of fluid loss. The principal regulator of extracellular water is sodium, because of active transport of sodium into this space. The principal regulator of the larger intracellular compartment is the effective osmolarity of the extracellular fluid. By osmosis, essentially equal tonicity is maintained across both compartments. Intravascular volume depletion leads to hypotension, compensatory tachycardia, decreased tissue perfusion and shock. The intravascular volume is highly protected to prevent these complications, primarily regulated by a sodium pump. Water is transferred to the intravascular volume from the extracellular compartment and the intracellular compartment.

Loss from the extracellular compartment is termed intravascular volume depletion and loss from the intracellular compartment is termed dehydration. Loss from both compartments is termed hypovolaemia.

Water loss

Water can be lost from the body via renal, cutaneous, respiratory and gastrointestinal routes. The kidney is the main controller of body water. The kidneys filter about 150 l of fluid per day, but only about 1% (1.5 l) is excreted as urine. Cutaneous water loss, through sweating, is a major thermoregulatory mechanism. Large amounts of heat are dissipated by sweat. The volume of water loss is usually around 500 ml per day, but can increase substantially in the presence of fever, high environmental temperatures, increased physical activity, increased metabolism or burns. A relatively small amount of water (around 200 ml per day) can be lost through respiration. This loss is affected by ventilatory volume and the environmental relative humidity. A large amount of water passes through the intestines each day and is recovered by the colon. Because of this, a relatively small amount of water (about 100 ml per day) is lost through faeces. However, gastrointestinal loss can increase significantly in the presence of diarrhoea, vomiting or other gastrointestinal pathology and cause severe dehydration.

Regulation of water balance

The balance between water loss and water repletion is regulated by arginine vasopressin (AVP). AVP works as an antidiuretic hormone, thereby regulating water excretion, and also by stimulating thirst, which regulates water ingestion. This balance is so carefully maintained that the osmolarity varies only between 282 and 298 milliosmoles (mOsm) per kilogram. Disorders of this careful balance can lead to severe illness and death.

AVP, the main water-regulating hormone, is controlled by osmotic sensors in the hypothalamus, and to a lesser extent by baroreceptor (pressure) signals. AVP levels increase rapidly with small increases in osmolality and produce sensations of thirst. The osmotic level for stimulation of AVP appears to be 284 mOsm kg^{-1}, with sensations of thirst appearing at a threshold of 294 mOsm kg^{-1}.[2] However, the data suggest that other non-osmotic triggers for thirst occur when the osmolarity is in the normal range. Moreover, there appears to be an individual set point that varies from person to person.[3]

Increased water loss due to exposure to heat, fever, insufficient fluid consumption and physical activity results in an increase in osmolality and a decrease in plasma

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

volume (hyperosmotic hypovolaemia), the main cause of dehydration. In such situations, dehydration stimulates both thirst and increases in AVP levels. This results in thirst, which increases fluid ingestion (when access is available), and a decrease in urinary output due to increased tubular water reabsorption in the nephron. Because of urine concentration, the urine becomes a darker yellowish colour. Changes in urine colour, urine osmolality and urine specific gravity have been used estimate levels of hydration.

The act of drinking rapidly suppresses the release of AVP, through a reflex mechanism in the oropharynx. Water balance is also affected by changes in intravascular volume. A loss of about 10% of circulating intravascular volume also stimulates the osmoreceptors. Loss of intravascular volume directly stimulates thirst and water intake through baroreceptors located in the vascular system. The renin–angiotensin–aldosterone system is also activated by stimulation of the baroreceptors, with the effect of increasing salt intake.

Negative feedback loops operate in conjunction with these systems. Osmotic dilution shuts off the thirst stimulus and AVP secretion. Continued osmotic dilution also stimulates the renin–angiotensin–aldosterone system to retain sodium and restore osmolarity. The renin–angiotensin system controls salt intake and thereby controls intravascular volume. Other hormones include atrial natriuretic peptide, which has a negative feedback to decrease AVP secretion and the renin–angiotensin–aldosterone system. Urodilatin and the oropharyngeal swallowing reflex also appear to play a role. A simplified diagram of volume regulation is shown in Figure 18.1.

Water regulation in older adults

In older persons, the regulation of water balance appears to be impaired. There is a diminished thirst response to in older persons to water deprivation[4] or infusion of hypertonic saline.[5] When older and younger men were restricted in water intake over a 24 h period that produced equal

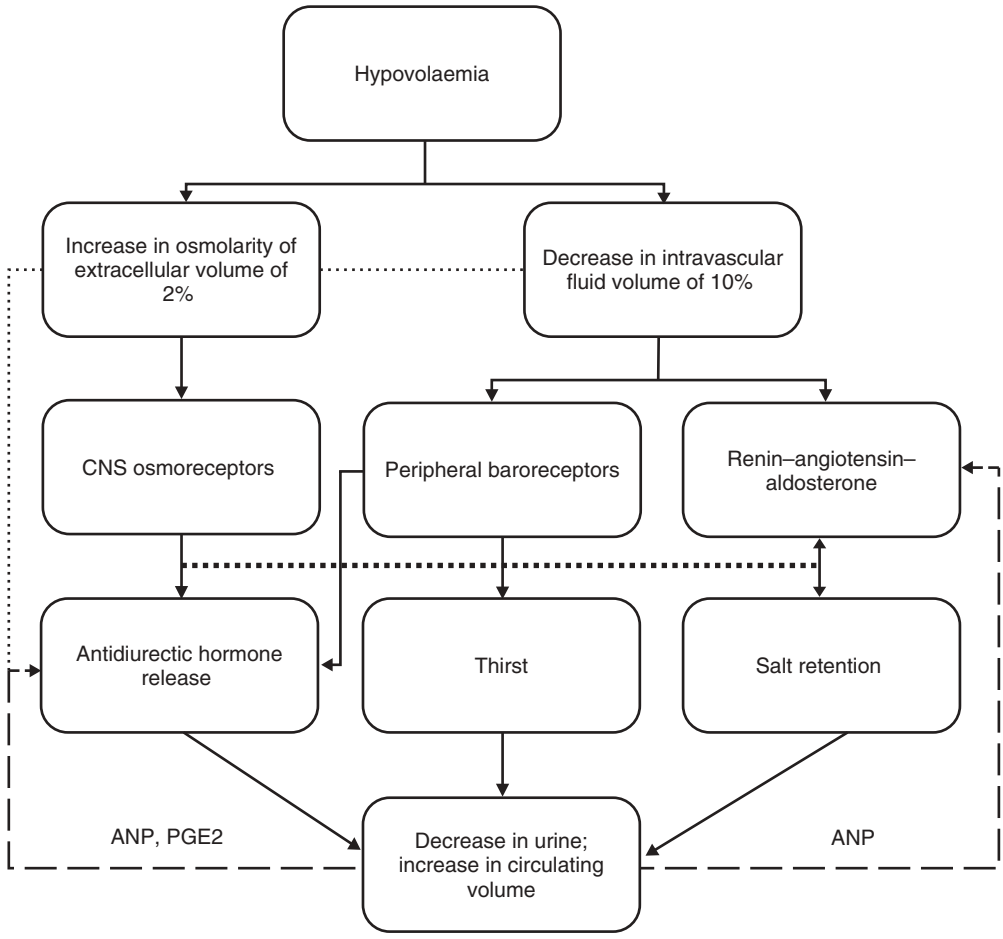

Figure 18.1 Simplified regulation of water balance. CNS = central nervous system; ANP = atrial natriuretic peptide; PGE2 = prostaglandin E2.

weight loss, healthy men aged 67–75 years were less thirsty and drank less water over 2 h compared with younger men.[6] In studies using heat stress and exercise to induce hyperosmolarity and a volume deficit, older individuals tended to operate at a higher plasma osmolality, indicating a shift in the set point of the regulatory system.[7] Again, the perception of thirst was not different in older men. Other studies have found that older men perceived a greater thirst, but drank the same amount of water as younger men in response to passive heat stress.[8]

In the face of water loss producing either an osmoreceptor or a baroreceptor stimulus, older persons exhibit a decreased thirst sensation and reduced fluid intake. Fluid replacement is effective but slower in older persons. Chronic fluid maintenance in response to repetitive dehydration also appears to be reduced, contributing to a decrease in the ability to expand plasma volume. The age differences in the physiological control systems associated with dehydration are more closely associated with a decrease in thirst perception. The data suggest that there is a higher osmotic operating point for thirst sensation under normal daily conditions and a diminished sensitivity to thirst triggered by the vascular baroreceptors.[9]

Dehydration, intravascular fluid loss and hypovolaemia

Physiologically, the term dehydration refers specifically to a decrease in intracellular water. A loss in the intravascular compartment results in intravascular volume depletion. Loss of both intracellular water and intravascular water is more appropriately termed hypovolaemia. Dehydration is always hypernatraemic, whereas intravascular volume depletion can be either hypernatraemic, hyponatraemic or isotonic.

Hypertonic intravascular volume depletion results when water losses are greater than sodium losses. Fever results in loss of water through the lungs and skin and, when combined with limited ability to increase oral fluid intake, is perhaps the most common cause of hypernatraemic intravascular volume depletion. As water is transferred from the intracellular compartment to maintain intravascular volume, total body water decreases, causing dehydration. Characteristic laboratory parameters include hypernatraemia (serum sodium levels $>145\,\text{mmol}\,\text{l}^{-1}$) and hyperosmolality (serum osmolality $>300\,\text{mmol}\,\text{kg}^{-1}$).

Isotonic intravascular volume depletion results from a balanced loss of water and sodium, which can occur during a complete fast. Vomiting and diarrhoea, because of large amounts of both water and electrolytes in gastric contents, will result in isotonic dehydration.

Hypotonic intravascular volume depletion occurs when sodium loss exceeds water loss. This type of dehydration occurs primarily with overuse of diuretics causing excess loss of sodium. The serum sodium is decreased ($<135\,\text{mmol}\,\text{l}^{-1}$) and the serum osmolality is low ($<280\,\text{mmol}\,\text{kg}^{-1}$).

Diagnosis of dehydration

There is no accepted definition of dehydration. A number of parameters have been used to suspect or define dehydration, but all have limitations.[10]

Body composition

The components of body water can be accurately measured by research techniques such as radiological dilution. Bioelectrical impedance[11–13] can determine total body water and extracellular water, estimating the intracellular water by subtraction. Bioelectrical impedance is based on the fact that fat-free mass has a much greater electrical conductivity than fat mass. However, the standard error of the fluid compartment estimates may be as high as ±2 l. Moreover, these modalities may not be readily available in clinical settings.

Body weight

A useful definition of dehydration is a loss of ≥3% of body weight. However, this presumes knowing the stable body weight prior to dehydration. This is useful in athletes and younger persons, but is not practical in older individuals. Weight fluctuations due to disease or drugs may be misleading, and at the lower body weights in older persons may be a total of 3–4 lb (~1.3–1.8 kg), which is in the standard error of measurement of most scales.

Physical examination

The physical signs of dehydration are often confusing, particularly in older adults. Clinical signs of extravascular volume deficit are often misleading. The most helpful physical findings are either severe postural dizziness such that the patient cannot assume an upright position or a postural pulse increment of $30\,\text{beats}\,\text{min}^{-1}$ or more. The presence of either finding has a poor sensitivity for moderate intravascular volume depletion due to blood loss (22%) but a much greater sensitivity for large blood loss (97%). Supine hypotension and tachycardia are frequently absent in extravascular fluid loss, and the finding of mild postural dizziness has no proven value. The presence of a dry axilla supports the diagnosis of dehydration [positive likelihood ratio, 2.8; 95% confidence interval (CI), 1.4–5.4], and a moist mucous membrane and a tongue without furrows argue against the presence of dehydration (negative likelihood

ratio, 0.3; 95% CI, 0.1–0.6 for both findings). In adults, the capillary refill time and poor skin turgor have no proven diagnostic value.[14]

Laboratory parameters

Given the paucity of sensitive clinical signs, laboratory evaluation provides the clinical gold standard. The diagnosis of extracellular volume depletion can be suspected from history and careful physical examination, but requires support of adjunctive data from laboratory studies. The diagnosis of intracellular volume depletion cannot be established without laboratory analysis of serum sodium or calculation of serum tonicity.[15]

Serum osmolarity is very sensitive, rising in dehydration with as little as a 1% change in body weight.[16] During dehydration due to insufficient fluid intake, both plasma sodium and osmolarity are significantly elevated. Serum osmolarity can be measured directly or estimated by the following formula:

$$2 \times (\text{serum sodium} + \text{serum potassium}) + [\text{blood urea nitrogen(BUN)} \div 2.8] + (\text{serum glucose} \div 18)$$

The ratio of BUN to serum creatinine has been used to estimate intravascular volume depletion. A ratio of >20–25 is variably used to define intravascular volume depletion. This ratio may be useful in children or in healthy adults, but is less useful in older adults due to the high incidence of renal disease. For example, a ratio of BUN to creatinine >5 when the increased ratio is due to an elevation in BUN with a normal serum creatinine indicates intravascular volume depletion. However, the same ratio when both the BUN and creatinine are elevated is more likely due to renal disease. Furthermore, the BUN may be low due to low protein intake or liver disease, and the serum creatinine may be low due to muscle wasting, thus limiting the usefulness in determining hydration status.

Urine colour

An eight-level urine colour scale is a reasonable index of hydration in athletic and industrial settings or in research studies using healthy individuals.[17] However, in sick individuals, only a weak relationship between urine colour and urine output has been demonstrated. No correlation between urine colour and body weight change, plasma osmolality or urine specific gravity has been observed.[18]

Problems with the diagnosis of dehydration

Some of the difficulty in the diagnosis of dehydration is in confusion over terminology. Dehydration is often inappropriately used as a non-specific generic term referring to any derangement in any fluid compartments. Clinicians often use the term dehydration when they mean intravascular volume depletion.[15] Furthermore, a diagnosis of dehydration is often inappropriately applied as a medical reason for hospitalization primarily resulting from social considerations.[19]

The diagnosis of dehydration is often made in the face of laboratory data which do not support the diagnosis. At best, this results in a mislabelling of the patient's condition. At worst, the diagnosis results in the inappropriate use of intravenous rehydration therapy.

In a study of the dehydration among hospitalized subjects,[20] a clinical diagnosis of dehydration was made on admission to the hospital in 21% of subjects. Of the patients who had a clinical diagnosis of dehydration on admission, only 19% had a serum osmolarity $>295\,\text{mOsm}\,\text{kg}^{-1}$, only 53% had a BUN/creatinine ratio >20 and only 17% had a serum sodium level $>145\,\text{mg}\,\text{l}^{-1}$. At least half of the diagnoses of either dehydration or intravascular volume depletion were incorrect based on laboratory data. This suggests that very few subjects had criteria for intracellular volume depletion (dehydration) and that clinicians are using the term synonymously with intravascular volume depletion.

During hospitalization, a diagnosis of dehydration was made in 79% of subjects. In these subjects, only 11% had a serum osmolarity $>295\,\text{mOsm}\,\text{kg}^{-1}$, only 50% of subjects had a BUN/creatinine ratio >20 and only 7% had a serum sodium level $>145\,\text{mg}\,\text{l}^{-1}$. Neither a serum osmolarity $>29\,\text{mOsm}\,\text{kg}^{-1}$ or serum sodium level $>145\,\text{mg}\,\text{l}^{-1}$ was present in 47% of subjects. Hence more than half of the subjects given a diagnosis of dehydration during hospitalization did not have confirmatory laboratory data for the diagnosis.

In subjects older than 65 years in this study, dehydration was the primary diagnosis in 26%. In these patients, 80% did not have a serum osmolarity $>295\,\text{mOsm}\,\text{kg}^{-1}$, 39% did not have a BUN/creatinine ratio >20, 77% did not have a serum sodium level $>145\,\text{mg}\,\text{l}^{-1}$ and 31% did not have either a BUN/creatinine ratio >20 or a serum sodium level $>145\,\text{mg}\,\text{l}^{-1}$. This suggests that the admission diagnosis of dehydration was not confirmed by laboratory data in almost one-third of subjects, using any combination of parameters for the diagnosis.

It is difficult to assess the frequency of dehydration due to variations in the definition in published studies. In community-dwelling older adults, the prevalence of dehydration ranged from 0.5% for hypotonic hypovolaemia (defined as a plasma tonicity $<285\,\text{mOsm}\,\text{l}^{-1}$ with orthostatic hypotension) to 60% with hypertonic hypovolaemia (defined as either a plasma sodium level $>145\,\text{mg}\,\text{l}^{-1}$, BUN/creatinine ratio >20 or tonicity $>295\,\text{mOsm}\,\text{l}^{-1}$), or hypotonic hypovolaemia. The elevated

osmolarity and BUN/creatinine ratio in this observational study were associated with chronic disease and functional impairment.[21]

Using only a BUN/creatinine ratio >20 produces extremely high prevalence rates of dehydration. In an emergency department study, 48% of persons over the age of 75 years were diagnosed as dehydrated on admission. However, less than 3% of subjects had a serum sodium level >145 meq l^{-1}, a percentage much closer to other published reports.[22] When unadjusted for other contributing causes, a BUN/creatinine ratio should probably not be used as the sole criterion for a diagnosis of dehydration.

Older persons appear to have a higher set point for osmolarity than younger persons. In a small sample of institutionalized older men followed for 6 months, 40% of the men had at least one serum osmolarity >295 mOsm kg^{-1}. About 20% of men had a serum osmolarity >300 mOsm kg^{-1}, but none had a concurrent serum sodium level >146 mg l^{-1} or a BUN/creatinine ratio >25. The BUN/creatinine ratios ranged from 12 to 34 over the 6 months, with 20% demonstrating elevated ratios consistently throughout the study without clinical evidence of dehydration. Only two patients had both an elevated serum osmolarity and serum sodium level, although both had a normal BUN/creatinine ratio. A normal serum sodium level was maintained in only 60% of the men throughout the 6 months. None of the men had clinical signs of dehydration at any time. These data suggest that in clinically stable long-term care residents, frequent elevations of serum osmolarity occur without overt clinical evidence of dehydration or an accompanying elevated sodium level or BUN/creatinine ratio.[23]

Consequences of dehydration

The diagnosis of dehydration has severe consequences. First, the diagnosis of dehydration is associated with an increase in hospital morbidity and mortality. Among patients with a diagnosis of dehydration admitted to an acute care hospital, the mortality rate was 30%. Hypernatraemic dehydration, defined as a serum sodium levels >145 meq l^{-1} and BUN >25 mg dl^{-1} with serum creatinine <3 mg dl^{-1}, was 2.9%. Subjects older than 85 years had a higher prevalence (5.3%) compared with subjects younger than 65 years (1.6%). A higher mortality (33%) was observed in subjects with a sodium level of 151–153 meq l^{-1}, and an even higher mortality rate in subjects with serum sodium levels >154 meq l^{-1} (71%).[24] Dehydration has been shown to increase by twofold the hospital mortality in patients admitted with stroke,[25] to produce a twofold increase in risk of pressure ulcers[26] and to increase the length of hospital stay in patients with community-acquired pneumonia.[27]

The mortality from dehydration may reflect the underlying disease state rather than a primary disorder in water regulation. In an acute care geriatric unit, 11% of subjects developed a plasma osmolarity of ≥320 mOsm l^{-1} in the 6 months following admission. In-hospital mortality was 35% in the hyperosmolar patients compared with 17% in non-hyperosmolar subjects. Diabetic hyperosmolarity accounted for most of these subjects, whereas hyperosmolar states developed in other subjects in association with infection, cognitive impairment and renal or cardiovascular disease. Impaired functional mobility was a risk factor for in-hospital mortality but not the degree of hyperosmolarity.[28]

Hyperosmolality is either a marker for, or a cause of, increased mortality in frail elderly patients. In a geriatric continuing care unit, the short-term survival of those patients with an osmolality >308 mOsm kg^{-1} was reduced and an increased mortality at 2 years was observed. However, there was no correlation between age and plasma osmolality.[29]

Second, the diagnosis drives the clinical approach to fluid therapy. The choice between resuscitation of the extravascular or intravascular fluid compartments may lead to inadequate fluid management or overhydration. In haemodynamically compromised individuals with orthostatic hypotension and oliguria, replacement with isotonic saline until haemodynamic stabilization is crucial.[30] Overzealous rehydration and improper monitoring may result in congestive heart failure and death in older persons.[31]

Finally, dehydration has been proposed as one of five quality of care indicators in long-term care. The diagnosis of dehydration in a patient admitted from a nursing home or from a home care setting may imply a failure in the quality of health care delivery.[32] However, the difficulty in diagnosing dehydration in older populations results in dehydration performing poorly as a quality of care indicator.[33]

Treatment of dehydration

The correction of dehydration lies in replacing water deficits. Water can be replaced orally, intravenously or by hypodermoclysis.[34] The total amount of estimated daily fluid requirements at baseline for adults older than 65 years is 30 ml kg^{-1} body weight. This requirement represents total dietary water, including that found in consumed foods. Water can be provided in any form, including free water, flavoured drinks or high water content foods. The amount of free water required to meet the 30 ml kg^{-1} per day requirement will be subtracted from the estimated amount of water contained in foods. For most enteral feeding products, about 75% of standard product serving is free water.

The type of oral replacement fluid should be selected based on the source of the water loss. For example, water loss due to extreme physical exertion, which includes loss of sodium and potassium, may require

solutions containing supplemental sugars, salt and potassium. Balanced solutions of water and electrolytes (e.g. sports drinks) may be more effective in fluid replacement under these circumstances. Water loss due to diarrhoea or vomiting likewise may require replacement of sodium and potassium. Oral rehydration formulae, which have been widely used in children, are effective for fluid replacement in older adults.[35]

The use of intravenous fluid replacement depends on the clinical diagnosis, the urgency of the situation or whether the patient is able to take oral fluids. For older persons presenting with dehydration due to free water deficits (e.g. febrile illness) and who are haemodynamically stable, replacement can be made with 5% dextrose in water (D5W). Replacement can be made at a rate of 25–30% of the estimated total free water deficit per day, although the exact rate of replacement depends on the acuity of the loss. Free water deficit (FWD) may be calculated by the following equation:[36]

$$\text{FWD (l)} = \text{weight (kg)} \times 0.45 - [(140/\text{measured serum sodium}) \times \text{weight (kg)} \times 0.45]$$

This equation is useful, but limited by the fact that the patient's baseline weight prior to becoming dehydrated must be known and used in the calculation.

Hypodermoclysis can be use as an alternative method of delivering fluids for patients who are stable and for whom intravenous access is not desired or difficult to establish. Isotonic or hypotonic solutions can be administered at a rate of 1 ml min^{-1} through needles inserted into the subcutaneous tissue of the abdomen or anterior or lateral thighs. Up to 1500 ml can be delivered through a single site and 3000 ml through two sites in 24 h.[37] Hypodermoclysis can produce tissue slough or abscess formation at the site and can result in over-hydration, just as with intravenous fluids.[38]

In persons with intravascular volume depletion who are haemodynamically unstable with significant volume loss (e.g. severe vomiting or diarrhoea), isotonic saline should be used until the patient is haemodynamically stable. Overzealous rehydration and improper monitoring can and do result in congestive heart failure and death in older persons. For this reason, careful monitoring of intravenous fluids and correct differential diagnosis is mandatory.

Prevention of dehydration

The requirement for water in older adults is controversial. Amounts range from 1 ml $kcal^{-1}$,[39] 30 ml kg^{-1} body weight[40] or the sum of 100 ml of fluid per kg for the first 10 kg actual body weight, 50 ml of fluid per kg for the next 10 kg actual body weight, and 15 ml of fluid per kg for the remaining kilograms actual body weight.[41] The first recommendation assumes normal caloric intake, the second recommendation depends on the person's body weight, which may not be normal, and the third recommendation attempts to adjust for current body weight. Direct observations of institutionalized adults indicate a total fluid intake, including fluids derived from meals, of 1783 ± 545 ml.[42]

All of the recommendations include water derived from all sources, including water from food sources. When the amount of water derived from food is subtracted, the most general recommendation for fluid intake (including free water) is 1500–2000 ml per day.[14]

Most older persons do not consume this amount of extra fluids/water. Most community-dwelling adults consume only about 1000 ml per day of fluids.[43,44] Institutionalized older persons may consume less.

Despite almost universal agreement that fluids need to be aggressively offered to older person, there are remarkably few data on prevention in the published literature. A meta-analysis found only two published intervention trials.[45] In a randomized, controlled trial of hydration intervention, the fluid intake of the experimental group exceeded that of the control group by a small amount. Bioelectrical impedance demonstrated a higher extracellular fluid volume (2.1 l), but no difference in total body water or intracellular water. No differences were detected in clinical outcome or confusional episodes between groups.[46]

Verbal prompting and specific beverage preference can increase fluid intake in most, but not all, incontinent long-term care residents. More cognitively impaired residents responded to verbal prompting, whereas less cognitively impaired residents responded to offering a beverage preference. The intensity of staff time was considerable over a 3 day intervention period.[47]

In summary, few data exist to support the assertion that dehydration can be prevented in older adults by close observation or interventional trials.

Conclusion

Water metabolism is carefully regulated and the consequences of dysfunction or disease are serious. Compared with normal physiological regulation, older adults appear to have alterations in thirst perception which are unrelated to arginine vasopressin secretion. Water replenishment after stimulation of the osmoreceptors or baroreceptors appears to be slower and not as complete as in younger persons. The calculated daily water requirement is 30 ml kg^{-1}, of which about 1500–2000 ml should be free water or fluids. Rehydration after water loss depends on the urgency of the need for replacement. Dehydration is common with concurrent disease in older persons and may appear quickly. Because of disordered thirst perception in older persons, encouragement to drink fluids may be necessary. However, older persons may not drink enough fluids to replenish

loss completely owing to a higher set point for their osmoreceptors.

Key points

- Dehydration lacks an accepted definition.
- Clinical signs lack sensitivity in the diagnosis of dehydration.
- Older persons have disordered thirst perception creating a propensity to become dehydrated.
- When oral or intravenous hydration presents problems, hypodermoclysis (subcutaneous fluid administration) has been used successfully.

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CHAPTER 19

Vitamins and minerals

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Introduction

The use of dietary supplements in general and nutrient supplements in particular is prevalent and growing in the United States. In 2007, dietary supplement sales grew to $23.7 billion. Sales of multivitamins, the most commonly purchased of supplements, grew by 3.9% in 2007 to $4.5 billion in sales for the year.[1,2] The ageing of the population and consumer desire to maintain good health and prevent disease have contributed to the increased growth of this industry. However, the current evidence on the use of dietary supplements rests on epidemiological association only.

The specific requirements for micronutrients in the elderly have not been studied until fairly recently. Vitamin and mineral requirements do not remain static over the adult life span. There are several micronutrients for which there is strong evidence that requirements are in fact increased in the elderly compared with younger people, such as vitamins D, B_6 and B_{12}.[3,4] It is clear that individuals change physiologically during ageing and that ageing is often associated with the development of chronic degenerative diseases. The roles that various supplements play in these changes appear to be less defined. There is an overall lack of evidence on the nutritional needs of the elderly, with a particular lack of data from clinical trials. Additionally, there is a critical need for the development of valid and reliable methods to detect undernutrition and for the generation of data to determine the dietary reference intakes (DRIs) of individuals 51–70 and >70 years old.[5]

Nutrition is an important determinant of health. As people age, activity levels and energy requirements tend to decrease. Concomitant decreases in food consumption may cause protein and micronutrient intake to fall below desirable levels. It is well documented that many older persons develop physiological anorexia associated with ageing. Additional factors that increase the risk of undernutrition include physiological changes that affect digestion, absorption and metabolism of nutrients, social isolation, chronic diseases, oral problems, sensory impairment, cognitive impairment, depression, multiple and chronic medication use, poverty and inappropriate food intake.[6–9]

Vitamin disorders in the elderly usually present atypically or are masked by coexisting diseases or a general failure to thrive.[10] Vitamin preparations are consumed on a daily basis by 20–60% of elderly people. These supplements are consumed for various reasons, including the following: to increase energy, improve health, improve appetite and prevent and treat diseases. Older persons may consume potentially toxic amounts of vitamins and minerals by supplementation.[11,12] Drug–nutrient interactions are common in the elderly because of the high incidence of polypharmacy, many of which may occur unrecognized.[13] Table 19.1 summarizes drugs with potential for interaction with various vitamins and minerals.

Prevalence/scope of the problem

There continues to be a lack of evidence on prevalence of vitamin and mineral deficiencies, most studies have concentrated on protein energy malnutrition.[15] The prevalence of vitamin deficiency in usual western diets is higher than generally believed, especially in the elderly.[16] Various studies have revealed that up to 20% of community-dwelling ambulatory adults, 37% of home-bound elderly, 30–60% of hospitalized patients and 17–85% of institutionalized patients are malnourished.[17–22]

According to the National Health and Nutrition Examination Survey (NHANES), up to 16% of Americans over the age of 65 years consume less than 1000 calories per day. The reduced caloric intake is incompatible with maintaining adequate vitamin and mineral intakes. Studies on vitamin deficiencies in older individuals have revealed that vitamin deficiencies vary from 2.6 to 6.8% for vitamin D in the general population to 35% in the institutionalized

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Table 19.1 Potential micronutrient–drug interactions.[10,14]

Micronutrient	Drug
Calcium	Vitamin D, lysine
Chromium	Vitamin C
Copper	Zinc, iron
Folic acid	Methotrexate, cotrimazole, phenytoin, sulfasalazine, triamterene, zinc, alcohol
Magnesium	Vitamin B_6, calcium
Manganese	Calcium, iron, zinc, copper
Selenium	Vitamin E
Vitamin A	Iron, vitamin E, tetracycline, cholestyramine
Vitamin B_1 (thiamine)	Vitamin B_2, vitamin B_3
Vitamin B_2 (riboflavin)	Ouabain, theophylline, penicillin, boric acid, probenecid, chlorpromazine, phenothiazines, barbiturates, streptomycin, oral contraceptives, antidepressants, probenecid, tobacco, alcohol
Vitamin B_3 (niacin)	Vitamin B_1, vitamin B_2, anticonvulsants, aspirin, clonidine, hydroxymethylglutaryl (HMG)-coenzyme A reductase inhibitors
Vitamin B_6 (pyridoxine)	Magnesium, anticonvulsants
Vitamin C	Copper, iron
Vitamin D	Aluminium hydroxide, corticosteroids, diuretics, rifampin, phenytoin
Vitamin E	Antacids, cholestyramine, colestipol, mineral oil, sucralfate, iron, vitamin A, tobacco, alcohol, coumarins, anticoagulants, indandiones
Vitamin K	Calcium, anticoagulants
Zinc	Diuretics, copper, *N*-acetylcysteine, iron, calcium, magnesium

Table 19.2 Prevalence of vitamin deficiencies in the elderly.

Vitamin	Independent (%)	Hospitalized (%)	Nursing home (%)
Vitamin A	1	Unknown	Unknown
Vitamin B_1 (thiamine)	13–43	40	2–5
Vitamin B_2 (riboflavin)	3–42	12	1–34
Vitamin B_6 (pyridoxine)	5–56	19	21–93
Folate	2.5–34	24	4–24
Vitamin B_{12} (cobalamin)	4–43	Unknown	4–29
Vitamin C (ascorbic acid)	Unknown	Unknown	0–5
Vitamin D	2–5	22	35

patients, while vitamin A deficiency is seen in 1% or less of the older adults. The prevalence for vitamin B deficiency shows marked heterogeneity. The prevalence for vitamin B_1 varies from <5% in the nursing home patients to as high as 43% in independent older persons; vitamin B_{12} deficiency is seen in up to 43% of independent older adults and in up to 29% of nursing home patients.[15,23–26] Table 19.2 gives the prevalence of vitamin deficiencies. Information on prevalence of trace mineral deficiencies comes from the developing world; zinc deficiency is widely recognized to be a common association with malnutrition. Geographic surveys show trends for selenium deficiency in individuals living in areas with low soil content of selenium.[27,28]

Dietary reference intakes

The goal of the Recommended Dietary Allowances (RDAs) was to estimate nutritional requirements for preventing basic deficiency diseases. The recommendations were also meant to be applied as general guidelines for groups, not as a gold standard for individuals. Research, led by the American Heart Association in the 1960s, demonstrated the links between diet and disease. It was already known that deficiency in certain nutrients results in disease. Studies went on to show clearly that increased intake of certain nutrients actually helps to prevent some chronic illnesses. Because of this research and because the RDAs were being used for purposes other than those for which they were created, new recommendations were in order.

The new guidelines are called *Dietary Reference Intakes* or *DRIs*. They were developed by the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, and published in 1998. These were designed to reflect the latest understanding of nutrient requirements based on optimizing health in individuals. For the first time, the group included data for individuals 70 years and older. They are being developed with individuals in mind. They are also concerned about the prevention of chronic degenerative diseases, such as macular degeneration, heart disease and osteoporosis. The DRIs are based on several factors. These include the level of a nutrient needed to meet the needs of a healthy individual and the level at which a nutrient will produce harmful side effects. The DRIs also consider the source of the nutrient, for example, the body is often better able to use nutrients supplied in food than by supplements. The new DRIs also take age and gender into consideration.[15,29–31]

The Board described four categories of reference values:
1 Estimated average requirement (EAR): represents the amount of nutrient intake that meets the requirements of 50% of the individuals in that group. The EAR serves as the basis for developing the recommended dietary allowance.

Table 19.3 Dietary reference intake for micronutrients (Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, 2010)[a].

Micronutrient	RDA/AI[b]				TUL			
	Age 51–70 years		Age >70 years		Age 51–70 years		Age >70 years	
	Male	Female	Male	Female	Male	Female	Male	Female
Vitamin A (μg)	900	700	900	700	3000	3000	3000	3000
Vitamin C (mg)	90	75	90	75	2000	2000	2000	2000
Vitamin D (μg)	15	15	20	20	100	100	100	100
Vitamin E (mg)	15	15	15	15	1000	1000	1000	1000
Vitamin K (μg)	*120*	*90*	*120*	*90*	ND	ND	ND	ND
Thiamine (mg)	1.2	1.1	1.2	1.1	ND	ND	ND	ND
Riboflavin (mg)	1.3	1.1	1.3	1.1	ND	ND	ND	ND
Niacin (mg)	16	14	16	14	35	35	35	35
Vitamin B_6 (mg)	1.7	1.5	1.7	1.5	100	100	100	100
Folate (μg)	400	400	400	400	1000	1000	1000	1000
Vitamin B_{12} (μg)	2.4	2.4	2.4	2.4	ND	ND	ND	ND
Calcium (mg)	1000	1200	1200	1200	2500	2500	2500	2500
Chromium (μg)	*30*	*20*	*30*	*20*	ND	ND	ND	ND
Copper (μg)	900	900	900	900	10000	10000	10000	10000
Fluoride (mg)	4	3	4	3	10	10	10	10
Iron (mg)	8	8	8	8	45	45	45	45
Selenium (μg)	55	55	55	55	400	400	400	400
Zinc (mg)	11	8	11	8	40	40	40	40

[a]RDA, recommended dietary allowance; AI, adequate intake; TUL, tolerable upper intake level; ND, not determined.
[b]AI values are in italic type.

2 Recommended dietary allowance (RDA): the daily nutrient intake that meets the nutrient needs of 97–98% of healthy individuals in that group. It is set at two standard deviations above the EAR.

3 Adequate intakes (AI): the average observed or experimentally derived intake by a defined population or subgroup that appears to sustain a defined nutritional state, such as normal circulating nutrient values, growth or other functional indicators of health.

4 Tolerable upper intake level (TUL): represents the maximum nutrient intake by an individual that is unlikely to pose risks of adverse health effects in 97–98% of individuals. It is not intended to be a recommended level of intake.

Table 19.3 gives the DRIs for vitamins and minerals for individuals aged 51–70 and over 70 years.

Factors affecting nutrient intake in the elderly

Total energy intake decreases substantially with age; this results in concomitant declines in most nutrient intakes, including vitamins and minerals. Despite the common occurrence of protein-energy undernutrition in older persons, its presence is rarely recognized. Factors implicated in the decreased nutrient intake in the elderly can be divided into the following categories:[32,33]

- social
- psychological
- medical
- age-related.

Factors affecting the nutrient intake are summarized in Table 19.4.

The antioxidants

One of the leading theories proposed for cellular and organism ageing is that damage to cellular mechanisms and tissues occurs because of chronic damage resulting from oxidative stress caused by oxygen free radicals. Endogenous oxidative damage to proteins, lipids and DNA is thought to be an important aetiological factor in ageing and development of chronic diseases such as cancer, atherosclerosis and cataract formation. The developing recognition that many disease states are caused by oxidative damage and that certain antioxidant compounds may scavenge these damaging oxygen free radicals has resulted in increased interest in vitamins and minerals as antioxidants. Vitamins A, C and E and β-carotene, referred to as *antioxidant vitamins*, have been suggested to limit oxidative damage in humans. Riboflavin (vitamin B_2) and selenium, a trace metal, are also suggested to have antioxidant capabilities.[10,32,34–36]

Table 19.4 Factors affecting nutrient intake in the elderly.

Social

1 Poverty
2 Social isolation
3 Ignorance
4 Problems with meal preparation
5 Inability to shop
6 Lack of recognition of ethnic or other food preferences in institutional settings
7 Monotony of institutionalized food

Psychological

1 Depression
2 Bereavement
3 Alcoholism
4 Dementia
5 Late-life paranoia
6 Late-life mania
7 Anorexia Tardive
8 Sociopathy
9 Overwhelming burden of life

Medical

1 Increased metabolism
   - Movement disorders: Parkinsonism and Tardive dyskinesia
   - COPD
   - Severe cardiac disease
2 Anorexia
   - Drugs: digoxin, psychotrophic drugs, theophylline, cimetidine, ranitidine, L-thyroxine
   - Gallstones, chronic and recurrent infections
   - Malignancy
   - Physiological anorexia of ageing
3 Swallowing problems
   - Oesophageal candidiasis
   - Teeth and denture problems
   - Severe tremors and strokes
4 Malabsorption
   - Late-onset gluten enteropathy
   - Lactose deficiency
5 Feeding problems
   - Severe tremor
   - Strokes
   - Dementia

Age related

1 Anorexia of ageing
2 Decreased olfaction
3 Decreased taste

A large body of epidemiological evidence suggests that eating a diet rich in sources of vitamins has a protective effect on development of disease. The strong association of dietary intake of vitamins and disease in epidemiological studies has not been borne out in clinical trials).[10] Caution must be exercised in interpreting the results of observational studies, as the association of diets rich in fruits and vegetables with reduced risk of cancer and cardiovascular disease may be due to the vitamins themselves, other compounds in fruits and vegetables or the substitution of dietary meat and fat with fruits and vegetables.[37]

Vitamin A and β-carotene

Vitamin A consists of preformed vitamin A (retinol) and the carotenoids such as β-carotene. The carotenoids are a diverse group of more than 600 naturally occurring pigments. Natural sources include yellow, orange and red plant compounds, such as carrots and green leafy vegetables. Humans cannot synthesize carotenoids and depend on dietary intake exclusively for these micronutrients. β-Carotene can act as an antioxidant by quenching the unpaired electrons of free radicals and divert free-radical damage towards itself. Vitamin A refers to preformed retinol and the carotenoids that are converted to retinol. Preformed vitamin A is found only in animal products, including organ meats, fish, egg yolks and fortified milk. More than 1500 synthetic retinoids, analogues of vitamin A, have been developed. Vitamin A intake decreases with age; however, hypovitaminosis A is uncommon even in the very old. The current RDI for vitamin A is 1500 $\mu g\,l^{-1}$(5000 IU). Except at the extreme ranges, retinol levels correlate poorly with vitamin A status and are affected by many non-nutritional diseases. Hepatic levels of vitamin A appear unchanged in adults. About 50–85% of the total body retinol is stored in the liver. It is also found in many other tissues in much lower concentrations.[10,32,38,39]

Dietary proteins undergo proteolysis to release retinyl esters in the stomach. They then join lipids and bile salts to form micelles for absorption through the intestinal mucosa. Preformed vitamin A is absorbed by the intestinal cell by a carrier-mediated mechanism, however; carotenoids are passively absorbed by the intestinal epithelium. Vitamin A is then transported to the liver via the lymphatics. By means of a receptor-mediated endocytosis on the surface of the hepatocytes, the retinol esters are released and stored as retinyl ester. These are further metabolized to combine eventually with retinol binding proteins (RBP) before storage in vitamin A-containing lipid globules within the hepatic stellate cells. In order for vitamin A to reach its target organs, it binds to RBP molecules for release into plasma as a retinol–RBP complex.[10,38–40]

Vitamin A has a number of biological actions. In the eye, it is required for prevention of xerophthalmia and phototransduction. Vitamin A is crucial to cellular differentiation and integrity.[40,41]

Vitamin A deficiency is rarely seen in the United States and other industrialized countries. However, it is still the third most common nutritional deficiency in the world. In the elderly, diminished physical activity reduces intake

and concentrations may drop, but there is little evidence to support the need for supplementation and, indeed, toxicity is manifested more readily with age.[38,40,42–44] Deficiency can result in the following:

- night blindness, complete blindness and xerophthalmia;
- Bitot's spots (areas of abnormal squamous cell proliferation and keratinization of the conjunctiva), which can be seen in young children;
- corneal perforation, keratomalacia and punctate keratopathy, which have been observed in early childhood development;
- non-specific dermatological problems, such as hyperkeratosis, phrynoderma (follicular hyperkeratosis) and the destruction of hair follicles and their replacement with mucous-secreting glands;
- impairment of the humoral and cell-mediated immune system via direct and indirect effects on the phagocytes and T cells.

In a majority of cases, vitamin A toxicity occurs because of the ingestion of large amounts of synthetic vitamin A, about 10 times higher than the RDI, or about 50 000 IU. In the elderly, diminished physical activity reduces intake and concentrations may drop, but there is little evidence to support the need for supplementation and, indeed, toxicity is manifested more readily with age. Hypervitaminosis can occur both acutely and after chronic ingestion. Symptoms of toxicity include dry skin, nausea, headache, fatigue, irritability, ataxia, alopecia, hyperlipidaemia, hepatotoxicity, bone and muscle pain and visual impairments.[10,40,41,45]

Epidemiological studies of dietary vitamin A on possible cancer chemoprevention appear to represent primarily the effect of α-carotene. Studies of relationships between cancer and vitamin A and carotenoids have provided mixed results. Observational data and clinical trial data have not been consistent.

Two large, randomized, placebo-controlled trials assessed the risk of lung cancer among male smokers or asbestos workers receiving α-carotene supplements. The risk of lung cancer was significantly increased among men receiving supplements. In the α-Tocopherol, α-Carotene (ATBC) Cancer Prevention Study, there was an increase in both prostate cancer incidence and mortality among subjects randomized to α-carotene. The excess risk appears to resolve over time once supplements are stopped.[46–48]

There have been no clinical trials of vitamin A intake and breast cancer. However, observational studies of vitamin A intake and breast cancer have yielded varying results. In a study by Kushi *et al.*, no association between dietary vitamin A and breast cancer was observed.[49] In contrast, recent data from the Nurses' Health Study suggest that premenopausal women, particularly those with a positive family history, have significant reductions in breast cancer risk with increasing dietary α-carotene and β-carotene, lutein/zeaxanthin and total vitamin A.[50,51] Data from the Polyp Prevention Study Group did not show a reduction in adenoma risk in patients randomized to receive either α-carotene, vitamin C and E or both α-carotene and vitamins C and E.[52]

Vitamin A and α-carotene supplements have shown no benefit for primary or secondary prevention of coronary heart disease (CHD) in randomized trials and have been associated with potential harm.[53] There is consistent evidence from observational studies that vitamin A intake within the range taken by many people in western societies, is a risk factor for osteopenia and fractures. The Physicians Health Study found that 12 years of α-carotene supplements had no effect overall on the risk of cataract formation, but appeared to decrease the risk significantly among current smokers.[54–57]

On the basis of current clinical data and the lack of clinical efficacy with respect to cancer prevention, along with its possible adverse effects, vitamin A and α-carotene supplement use should be discouraged.

Vitamin E

Vitamin E occurs in eight natural forms as tocopherols (α, β, γ and δ) and tocotrienols (α, β, γ and δ), all of which possess potent antioxidant properties. Vitamin E was originally found to affect reproduction in rats and was given the name tocopherol, derived from the Greek words *toc* (child) and *phero* (to bring forth) to describe its role as an essential dietary substance in normal fetal and childhood development.[58,59]

Vitamin E absorption depends on the breakdown of fatty acids and their uptake via enterocytes to the enterohepatic circulation. The synthesis of chylomicrons is required for transport of vitamin E via the lymphatic system to the liver. Within hepatocytes, chylomicron remnants are broken down by lysosomes and *R*,*R*,*R*-α-tocopherol is preferentially secreted into the bloodstream, packaged within very low density lipoprotein (VLDL) molecules. The transport protein for α-tocopherol is named α-*tocopherol transfer protein* (α-TTP).[60–62]

Vitamin E works as a free-radical scavenger and antioxidant. α-Tocopherol is the biologically active form of vitamin E. It protects polyunsaturated fatty acids (PUFAs), a major structural component of the cell membranes, from peroxidation. Primary sources of vitamin E are vegetable oil, wheat germ, leafy vegetables, egg yolk, margarine and legumes.[63,64] Vitamin E deficiency can be measured by examining serum or tissue α-tocopherol levels.[65]

Deficiency of vitamin E is uncommon in humans except in unusual circumstances. In the elderly, conditions resulting in fat malabsorption can cause vitamin E deficiency. The effects of deficiency are widespread throughout the body and include the following:[40,66,67]

- Neuronal degeneration resulting in spinocerebellar ataxia, decreased deep tendon reflexes or areflexia, peripheral neuropathy and posterior column destruction with impairment of proprioception and vibratory sense. This can result in gait disturbance, which is a basic manifestation of vitamin E deficiency.
- Degenerative myopathy.
- Ocular impairment such as retinopathy and extraocular muscle paresis.
- Brown bowel syndrome, a result of lipofuscin deposition and oxidative damage.
- Red blood cell life span reduction.

The effects of long-term supplementation of vitamin E are unclear. Some studies caution against the use of vitamin E in patients with an increased propensity to bleeding or those taking oral anticoagulants. Impaired absorption of fat-soluble vitamins A and K with large vitamin E supplements have been seen in animal models. Necrotizing enterocolitis is seen in infants supplemented with high doses of vitamin E. It may impair the haematological response to iron in children with iron-deficiency anaemia.[40,68,69]

The protective role of vitamin E against cancers seen in observational studies[49,51,70,71] has not been supported by randomized trials. The ATBC Cancer Prevention Study observed a 32% decrease in prostate cancer incidence and a 41% decrease in prostate cancer mortality among men receiving α-tocopherol compared with placebo.[72] A second report from the ATBC study showed a significant 19% reduction in lung cancer risk associated with higher serum vitamin E levels. The reduction in risk was greatest among men younger than 60 years and among patients with fewer years of cumulative smoking exposure.[73] The SELECT trial followed 35 533 relatively healthy men for a median of 5.5 years. Vitamin E supplementation did not prevent prostate cancer in this population.[74] The Physicians' Health Study II did not reveal any benefit of vitamin E supplementation on the incidence of prostate cancer.[75] The HOPE-TOO trial and the Women's Antioxidant Cardiovascular Study found no effect of vitamin E supplementation on cancer incidence or cancer deaths.[76a,77]

Vitamin E supplementation has shown no benefit in both primary and secondary prevention of CHD.[53] In the ATBC study, daily supplementation with vitamin E had no overall effect on stroke risk. However, a subgroup analysis suggested that vitamin E may increase the risk for subarachnoid haemorrhage and decrease the risk for ischemic stroke, particularly in men with hypertension.[78] In the Heart Outcomes Prevention Evaluation (HOPE) trial, daily supplementation with vitamin E had no effect on progression of carotid intimal medial thickness.[76b] The HOPE-TOO trial (ongoing outcomes) showed that vitamin E at 400 IU was associated with an increase in heart failure.[76a] The Health Professionals Follow-up Study showed no association between supplemental vitamin E and stroke risk.[79]

Data from observational studies have suggested that increased dietary intake of vitamin E may have a protective effect against the development of Alzheimer's disease. A longitudinal cohort study found that both vitamin E and C supplementation protected against the development of vascular dementia and improved cognitive function late in life.[80-82] A randomized trial of selegiline, vitamin E, both or placebo among patients with Alzheimer's disease showed that both selegiline and vitamin E were independently associated with significant reductions in several outcomes, including functional decline.[83] A randomized trial of vitamin E supplementation in healthy older women did not reveal any cognitive benefit.[84]

There have been several studies reporting that vitamin E supplementation improves the immune response. However, randomized, placebo-controlled studies have found no reduction in the incidence of respiratory infections in institutionalized or non-institutionalized elderly patients receiving daily vitamin E supplements.[85-89]

A meta-analysis of vitamin E supplementation that did not stratify trials by dose of vitamin E found no significant effect of supplementation on all-cause mortality.[53] However, a recent meta-analysis that examined the dose–response relationship between vitamin E and overall mortality in a total of 19 randomized clinical trials found that vitamin E supplementation with a dose of ≥400 IU per day was associated with a significantly increased risk of all-cause mortality.[90]

Current evidence for vitamin E supplementation is inconclusive. Data at present suggest that high-dose vitamin E (≥400 IU per day) increases all-cause mortality. Also, individuals taking anticoagulants should be particularly advised against high doses of vitamin E because of the synergistic action of vitamin E with these drugs.

Selenium

Selenium, a trace element, is a component of several enzymes, including glutathione peroxidase and superoxide dismutase. Both of these enzymes are important in the prevention of oxidative and free-radical damage to various cell structures. Evidence suggests that the antioxidant protection conveyed by Se operates in conjunction with vitamin E because deficiency of one seems to enhance damage induced by a deficiency of the other.[91] Se is incorporated as selenocysteine at the active sites of multiple selenoproteins. Selenoproteins are also important for thyroid function, muscle metabolism and sperm function, and also immune function.[92]

Dietary sources include vegetables, grains, Brazil nuts, seafoods and organ meats. The amount of Se in plant food is determined by the amount present in the soil. The mechanism of absorption of Se from the gut is unknown.

Dietary Se has a high bioavailability and its absorption from the gut is unregulated.[93,94]

The risk of Se deficiency seems to increase in proportion to age. Also, low levels have been documented in type II diabetes.[92,95] In China, Keshan disease is seen in areas where the soil is poor in Se. It is an endemic cardiomyopathy which improves with Se supplementation. Se deficiency has been reported in individuals on chronic total parenteral nutrition (TPN).[96] Severe deficiency of Se manifests as cardiomyopathy and myopathy.

Toxicity can result from excessive intake. The most common manifestations are hair and nail loss. Other manifestations include nausea, emesis, tooth lesions, mental status changes and peripheral neuropathy.[97,98]

The potential protective effect of Se status on the risk of developing cancer has been examined in animal and epidemiological studies. Low levels of dietary Se are associated with a greater risk of prostate, oesophageal, colon and antral gastric cancers.[93,99–101] There have been studies evaluating the effect of Se on cancer-related chemotherapy. A study assessing the *in vitro* effects of Se on chemotherapy revealed that the addition of Se enhanced drug-mediated cancer cell death. In another study, the addition of dietary Se at the beginning of chemotherapy prevented the development of resistance to cisplatin.[102,103]

The antioxidant properties of Se have been linked to a lower incidence of cardiovascular disease in humans. However, the therapeutic benefit of Se administration in the prevention and treatment of cardiovascular diseases still remains controversial.[104,105]

Se deficiency has been associated with impaired cell-mediated immunity and enhanced activity of natural killer cells.[106,107] Studies on the coxsackievirus and influenza virus by Beck and co-workers[108,109] have shown that Se prevented the genomic conversion of a non-virulent strain into a virulent strain that occurred in the presence of Se deficiency in mice. These effects of Se may have considerable implications on the elderly population, especially in the institutional setting.

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin widely found in citrus fruits, raw leafy vegetables, strawberries, melons, tomatoes, broccoli and peppers. Humans cannot synthesize vitamin C and a deficiency results in scurvy. The amount present in food consumed, however, depends on the season of the year, the transportation time to the store, the shelf time before purchase, the form of storage and the method of cooking. Boiling can cause a 50–80% loss of vitamin C. Cooking with minimal water or microwaving food reduces losses.[32,67]

Vitamin C is absorbed in the distal small intestine through an energy-dependent process. Blood concentrations of ascorbic acid are regulated by renal excretion. The greatest concentrations of ascorbic acid are found in the pituitary, adrenal, brain, leukocytes and the eye. Its absorption does not seem to be affected by age. The bioavailability of vitamin C is inversely related to the amount ingested and also the form. Sustained release tablets allow higher absorption than standard pills. It is a reversible biological reductant and provides reducing equivalents for a number of biochemical reactions involving iron and copper. It therefore functions as a cofactor, enzyme complement, cosubstrate or a strong antioxidant in a variety of reactions and metabolic processes.[10,110–113]

Vitamin C has multiple functions. It is an antioxidant and reduces harmful free radicals. It is purported to be an immune enhancer and is known to be crucial to collagen synthesis and to norepinephrine synthesis. The conversion of iron from the ferric (+3) to the ferrous (+2) form requires vitamin C. Without this conversion, methaemoglobin could not be converted to haemoglobin and iron could not be absorbed in the duodenum. Vitamin C is also involved in the reduction of nitrates, a function that possibly is involved in stomach cancer. Vitamin C has a role in prostaglandin and prostacyclin metabolism. It may be capable of attenuating the inflammatory response or even sepsis syndrome.[67,114–116]

Vitamin C deficiency is common in many frail elderly populations. Because vitamin C is supplied only by diet, deficiency is caused by insufficient dietary intake.[10,117–119] Deficiency primarily affects the musculoskeletal and haematopoietic systems. Deficiency results in the following:[67]

- Reduced collagen cross-linking and therefore decreased collagen tensile strength, leading to impaired wound healing and to weakened blood vessels.
- Haemostasis abnormalities occur, producing painful subperiosteal haemorrhages, haemarthrosis, haemorrhagic perifolliculitis, gingival bleeding, ecchymoses, petechiae and nail bed splinter haemorrhages. Some of these manifestations are common in elderly persons and are usually attributed to age-related physiological changes and not to vitamin deficiency.
- Structurally abnormal collagen that produces structurally abnormal osteoid, which produces structurally abnormal bone.
- Scurvy, which is the clinical syndrome produced by deficiency and develops after intake of less than 10 mg per day for 3–6 months. Scurvy includes the previously mentioned physical findings plus the development of corkscrew hairs, glossitis, gingival hyperplasia and bleeding and poor dentition caused by periodontitis and loss of teeth. Iron-deficiency anaemia can also occur. Terminal features include icteris, oedema, hypotension and convulsions.

There have been some reports of excessive use of vitamin C as a risk factor for calcium oxalate nephrolithiasis.

However, a prospective epidemiological study demonstrated that consumption of high doses of vitamin C lowered the relative risk of calcium oxalate stones compared with 250 mg or less of vitamin C per day. Ingestion of large quantities of vitamin C has been rarely associated with fatal cardiac arrhythmias in patients with iron overload, presumably due to oxidative injury. Vitamin C toxicity has been associated with diarrhoea and abdominal bloating. High doses are also associated with false negative guaiac tests and they also alter the results of glucose measurements.[116,120–122]

A large, randomized trial of vitamin C for secondary prevention of CHD found no benefit of supplementation with vitamin C. The Health Professionals Follow-up Study showed no association between supplemental vitamin C and stroke risk. Prospective data from the Nurses' Health Study showed a 45% reduction in the risk of cataract requiring extraction in women using vitamin C supplements for at least 10 years. In contrast, a randomized, placebo-controlled study of high-dose supplementation with vitamins C and E and β-carotene found no reduction in the 7 year risk of development or progression of age-related lens opacities with vitamin C supplementation.[53,79,123,124]

Riboflavin

Riboflavin or vitamin B_2 is an important component of the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). It is involved in an array of biochemical reactions. It is important for oxidative phosphorylation, ATP production and the production of reduced glutathione, which is an antioxidant. Vitamin B_2 has been implicated in a signal transduction role for programmed cell death and regulation of a number of other important intracellular pathways. Dietary sources include dairy products, green leafy vegetables, whole and enriched grains, meats, liver, poultry and fish. It is not destroyed by heat, oxidation or acid but is susceptible to ultraviolet light and alkalis.[67,125]

Riboflavin is released by proteolysis from the ingested food and undergoes passive absorption from the intestinal lumen. It then enters the hepatic cells and undergoes conversion to FAD and FMN. Like other B vitamins in this class, stores are minimal and regulated replacement is necessary through food or supplements.

Vitamin B_2 deficiency is regarded as the most common vitamin deficiency in the United States; it is usually seen in conjunction with other B vitamin deficiencies. There is some evidence that the requirements for riboflavin may increase with ageing and that the glutathione reductase activity declines with ageing. Plasma riboflavin concentrations tend to reflect recent dietary intake. Erythrocyte glutathione reductase assay is a better test for riboflavin deficiency; it is not valid, however, in individuals with glucose 6-phosphate dehydrogenase deficiency.[15,91,125]

Deficiency may be secondary to inadequate dietary intake or a result of chronic diarrhoea, alcoholism or liver disease. Deficiency may manifest as the following:[67,91,125]

- cheilosis
- magenta-coloured glossitis
- inflammation of the oral mucosa
- seborrheic dermatitis
- normocytic normochromic anaemia
- corneal revascularization.

Vitamin B_2 supplementation helps only in the prevention of deficiency. A small randomized controlled trial has shown some benefit of supplementation with a very large dose in the prevention of migraine.[67,126]

Vitamin D

Vitamin D, or calciferol, is a generic term and refers to a group of lipid-soluble compounds with a four-ringed cholesterol backbone. Vitamin D is not a true vitamin, because humans are able to synthesize it with adequate sunlight exposure. By photoconversion, 7-dehydrocholesterol becomes previtamin D_3, which is metabolized in the liver to 25-hydroxyvitamin D3, the major circulating form of vitamin D. In the kidneys, this is converted to two metabolites, the more active one being 1,25-dihydroxyvitamin D_3. It is derived primarily via synthesis in the skin. Dietary sources include fortified milk, milk products, oily fish, egg yolks and fortified foods.[32,40,67]

Vitamin D is absorbed in the form of micelles by the intestinal epithelium to form chylomicrons. Chylomicrons enter the liver via the portal circulation where vitamin D undergoes a hydroxylation process by 25-vitamin D hydroxylase to form 25-hydroxyvitamin D (calcidiol). Further hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [1,25$(OH)_2$-vitamin D or calcitriol] occurs in the mitochondria of the proximal tubules of the kidney. Vitamin D from any source and in either form is absorbed into the circulation and bound to vitamin D-binding protein. Calcitriol, the biologically active form, has a short half-life of 4–6 h and therefore does not accurately reflect body stores, whereas calcidiol has a longer half-life of 3 weeks. Hence calcidiol is more widely used to measure vitamin D status. Laboratory measurements reflect both vitamin D_2 and vitamin D_3 status. Deficiency is defined as a calcidiol level below 15 mg dl^{-1}.[40,67,127–129]

Increased age is a risk factor for vitamin D deficiency. Several studies have shown that the levels of calcitriol are lower in older people.[3,130] Calcidiol was shown to decline with age in a longitudinal study by Perry *et al*.[131] Factors resulting in low circulating levels in the elderly include the following:

- inadequate intake of vitamin D due to decreased intake of dairy products in their diets;
- decreased ability to form previtamin D_3 in the skin upon ultraviolet light exposure secondary to decreased amounts of 7-dehydrocholesterol levels in the skin with advancing age;
- decreased synthesis of 1,25-dihydroxyvitamin D by the kidney;
- medications interfering with vitamin D metabolism.

Deficiency of vitamin D can result in the following biochemical and physical manifestations:[67]

- low calcium and phosphorus levels and elevated alkaline phosphatase levels;
- secondary hyperparathyroidism;
- osteomalacia;
- fractures;
- neuromuscular irritability;
- proximal myopathy, deep proximal musculoskeletal pain, neuropathy and hyperaesthesia.

Vitamin D excess is associated with hypercalcaemia, hypercalciuria, confusion, polyuria, polydipsia, anorexia, vomiting, muscle weakness and bone demineralization with pain.[40]

A prospective, population-based study showed that lower calcidiol and higher PTH levels increased the risk of sarcopenia in older men and women.[132a] In a case–control study of community-dwelling women, low serum calcidiol concentrations were associated with a higher risk for hip fracture.[132b] Several studies have shown decreased risk of falls in both ambulatory and institutionalized elderly people receiving vitamin D supplementation. However, these studies revealed that the reduction in fall risk is dose dependent and doses lower than 600 IU per day do not reduce the risk for falls.[133,134] A systematic review and meta-analysis of vitamin D supplementation in older adults found that the relative risk of fall was 0.86 (95% CI 0.79–0.93) for those assigned to vitamin D therapy (200–1000 units) compared with placebo. This study included 10 trials in both community and institutional settings in which the fall outcome was explicitly defined.[135] A recent randomized controlled trial using high-dose oral vitamin D supplementation in community-dwelling older women showed an increased incidence of falls in the first 3 months following supplementation.[136] A number of trials have reported a beneficial effect of calcium or calcium plus vitamin D on bone density in postmenopausal women and older men. The data on vitamin D supplementation and fracture rates are more variable.[137–142] A subgroup analysis of the Women's Health Initiative Study revealed that calcium and vitamin D supplementation was associated with reduced fracture incidence in those subjects who were most compliant.

Current evidence, mainly from observational studies, reveals a link between vitamin D supplements and other disease states. Observational studies in humans suggest a link between poor vitamin D status and the risk of nearly all cancers.[143,144] However, the association of vitamin D status with cancer appears to be greatest with colon cancer.[145,146] Also, data from case–control studies indicate a reduced risk of type 1 diabetes with vitamin D supplementation.[147] The Women's Health Initiative Study, revealed an association between higher total vitamin D intake and lower risk for type 2 diabetes.[148] The association of vitamin D status with cardiovascular outcomes has revealed an inverse relation between calcidiol and cardiovascular disease.[149] Low levels of calcidiol have frequently been noted in patients with Alzheimer's disease. In one study, low levels of vitamin D were associated with an increased risk of cognitive decline.[150] At the present time, there is insufficient evidence supporting vitamin D supplementation for prevention or treatment of cancer, diabetes, cardiovascular diseases or cognitive decline.

The daily intake of vitamin D in older adults should be at least 800 IU with at least 1200 mg of elemental calcium in the diet or as a supplement.[40] This is particularly important in the elderly individuals who are unable to expose themselves to sunlight, since a large part of the daily requirements are met by skin synthesis.

Vitamin K

Vitamin K occurs in two naturally occurring forms, phylloquinone found in plants and menaquinones synthesized by the gastrointestinal flora. Vitamin K produced by the gut flora is thought to provide up to 50% of the requirement in humans. Vitamin K is found in various food sources, including green leafy vegetables, vegetable oils and liver[67,151]

Vitamin K is a fat-soluble vitamin absorbed by the intestinal epithelium in the form of micelles. It is then incorporated in chylomicrons and enters the liver via the portal circulation. Within the body, the stores are relatively small. They are mostly hepatic; however, the trabecular and cortical bone also contain substantial concentrations.[40,151]

Vitamin K is an important cofactor for the endoplasmic enzyme γ-glutamylcarboxylase. This enzyme acts as a catalyst for the carboxylation of glutamate to γ-carboxyglutamate. This is an important step for the activation of several coagulation factors within the hepatic cells. It thus plays a central role in blood coagulation, by activating factors II, VII, IX and X. It is also needed for the activity of the natural anticoagulants proteins C and S.[40,67,151]

Deficiency of vitamin K in healthy adults is uncommon because of the widespread distribution of the vitamin in Nature, its recycling within the cells and its synthesis by the gastrointestinal flora. Deficiency can be seen in the following conditions:[40,67,151,152]

- prolonged antibiotic therapy, which disrupts the gastrointestinal flora;
- parenteral nutrition;
- disorders associated with fat malabsorption;
- medications such as anticonvulsants, high doses of vitamins A and E, warfarin;
- starvation.

Deficiency results in prolongation of the prothrombin time and partial thromboplastin time and signs and symptoms of bleeding such as easy bruisability, splinter haemorrhages, mucosal bleeding, melena and haematuria.[40,63,67,151,152] Studies have shown an increase in the incidence of hip fractures in the elderly. There have been studies showing a decrease in bone mineral density in hemiplegic limbs of vitamin D deficit stroke patients.[153,154]

Toxicity associated with excess doses is rare; it can, however, cause haemolytic anaemia and jaundice in infants. Doses greater than 150 μg per day from food supplements can interfere with anticoagulation in patients on warfarin.

Folate

Folates represent a group of related pterin compounds. More than 35 forms of the vitamin are found naturally. The term folic acid is derived from the Latin word *folium*, which means leaf. The pharmacological form is folic acid; it is more bioavailable and does not exist in Nature in this form. The various dietary sources include green leafy vegetables, fresh fruits, yeast, liver and other organ meats. Folate in foods is destroyed by excessive cooking; as much as 95% may be destroyed.[10,67,155]

Folate is required for the transfer of single carbon groups; it is essential in the *de novo* synthesis of nucleotides and metabolism of several amino acids. It is an important component for the regeneration of the 'universal' methyl donor *S*-adenosylmethionine. In the body, homocysteine is remethylated into methionine. The process of remethylation requires folate and cobalamin (vitamin B_{12}). In the presence of folate deficiency, homocysteine levels are elevated.[67,155]

The luminal enzymes convert the polyglutamate forms of folate present in the dietary sources to the monoglutamate and diglutamate forms. Folate is then absorbed from the lumen of the small intestine by both active and passive absorption. In the plasma, folate is present as 5-methyltetrahydrofolate; it is bound loosely to albumin, from which it is readily taken up by the high-affinity folate receptors present on cells throughout the body. Folates undergo enterohepatic circulation and are thus reabsorbed from the gut; they also undergo urinary excretion.[67,155]

Studies have revealed that folate deficiency may range from 2.5 to 34% among elderly persons. Folate deficiency occurs within a few days of insufficient intake; however, clinical signs of deficiency develop after ~4 months of decreased intake. Folate deficiency can be determined on the basis of decreased serum folate levels; however, red cell folate level may be a better indicator if there has been a recent dietary change. Factors responsible for deficiency in the elderly include the following:[10,15,67,155]

- inflammatory diseases of the gastrointestinal tract;
- atrophic gastritis;
- part of generalized malnutrition;
- poor oral intake;
- excessive alcohol intake;
- smoking;
- medications such as cotrimazole, methotrexate, triamterene, phenobarbital and phenytoin.

Folate deficiency can result in megaloblastic anaemia, leukopenia, thrombocytopenia, anorexia, fatigue, delirium, diarrhoea, glossitis and hyperhomocysteinaemia.

Current evidence suggests that high dietary intake of folate is associated with a decreased risk of developing colorectal cancer in both men and women. Data from the Nurses' Health Study reveal a protective effect of high dietary intake of folate on the development of breast cancer. There was a normalization in the risk of breast cancer associated with concurrent alcohol use.[156–158]

Folate deficiency is associated with hyperhomocysteinaemia. Homocysteine is prothrombotic and atherogenic. It causes vascular injury characterized by thickened vascular intima, disruption of the elastic lamina, smooth muscle hypertrophy, platelet aggregation and the formation of platelet-rich occlusive thrombi.[159,160] In a multicentre case–control study by Robinson *et al.*,[161] lower levels of folate and vitamin B_6 conferred an increased risk of atherosclerosis. The increased risk was explained partly by an elevated homocysteine level. In the Health Professional Follow-up Study, increased folate intake was associated with a decreased risk of ischaemic stroke in men.[162] In another study, an inverse association between a high-folate diet and coronary heart disease was found to be strongest among women who consumed up to one alcoholic beverage per day.[163] Data also suggest that there may be a correlation of high homocysteine levels with osteoporotic fractures and dementia.[164–166]

Vitamin B_{12}

Vitamin B_{12} is a group of cobalamin compounds that have a corrin ring with a cobalt atom at the centre. The corrin ring is connected through an aminopropanol bridge to a ribonucleotide. Dietary sources of vitamin B_{12} include meat and dairy products. It is an important cofactor for the enzymes methionine synthase and methylmalonyl-coenzyme A (CoA) mutase. It is essential for the synthesis of succinyl-CoA from methylmalonyl-CoA. Vitamin B_{12} serves as a cofactor in the conversion of 5-methylenetetrahydrofolate (5-methylene-THF) to THF (the active form of folate); during this reaction, the methyl

group is donated to cobalamin, forming methylcobalamin. Methylcobalamin then donates its methyl group to homocysteine to form methionine. The synthesis of methionine is essential for purine and pyrimidine synthesis, methylation reactions and the intracellular retention of folates. A deficiency of cobalamin leads to an increase in homocysteine and methylmalonic acid.[155,167]

Cobalamin is released from the food by the gastric enzymes and bound to R-binding proteins. Further, enzymatic degradation occurs in the small intestine and it then becomes bound to the intrinsic factor (IF). The vitamin B_{12}–IF complex is then absorbed in the ileum and stored in the liver. It is transported through the body attached to the protein transcobalamin II. Vitamin B_{12} undergoes enterohepatic circulation and most of it is reabsorbed from the bile.[10]

The prevalence of vitamin B_{12} deficiency ranges from 4 to 43%. The levels of vitamin B_{12} have been found to decline at the rate of 3.4 pmol l^{-1} annually. Vitamin B_{12} deficiency may be seen in the elderly population as documented by elevated methylmalonic acid with or without elevated total homocysteine concentrations in combination with low or low-normal vitamin B_{12} concentrations. Owing to the long half-life and hepatic stores of vitamin B_{12}, deficiency secondary to inadequate intakes takes 2–6 years to develop. Deficiency is seen in individuals with atrophic gastritis, total gastrectomy, pernicious anaemia (which may be seen in up to 5% of those aged 80 years and above in some populations), terminal ileal resection, bacterial overgrowth of the bowel, drug use such as prolonged use of H-2 antagonists, colchicines and aminosalicylic acid and practice of strict vegetarianism.[10,15,67]

Deficiency can result in the following:[67,155]

- increased homocysteine levels;
- increased methylmalonic acid levels;
- megaloblastic anaemia;
- neurological syndrome manifested as

  i peripheral neuropathy with paresthesias and decreased vibratory sensation, which may progress to ataxia, weakness and an inability to walk; it affects both the dorsal and lateral spinal cord columns and is termed *subacute combined degeneration*;

  ii impaired mentation, memory loss and depression. This syndrome may occur without evidence of anaemia and may not be associated with macrocytic erythrocytes.

Current evidence suggests an increased risk of cardiovascular disease associated with elevated homocysteine levels. Vitamin B_{12}, folate and vitamin B_6 are needed for homocysteine metabolism and deficiency results in elevated levels of homocysteine. Although studies have shown a decreased risk of cardiovascular disease with high levels of folate and vitamin B_6, this has not been shown with vitamin B_{12} supplementation.[32,168]

In a study by Lindenbaum *et al.*,[169] neuropsychiatric disorders due to cobalamin deficiency were seen in the absence of anaemia or an elevated mean cell volume. They recommended measuring serum methylmalonic acid and total homocysteine, both before and after treatment for diagnosis in these patients.

Vitamin B_{12} supplementation should be considered in the elderly and at-risk individuals.

Vitamin B_6

Vitamin B_6 comprises various derivatives of pyridine, including pyridoxine, pyridoxal and pyridoxamine. As a coenzyme, vitamin B_6 is involved in many transamination reactions. It is required for the synthesis of niacin from tryptophan. Vitamin B_6 is involved in the synthesis of several neurotransmitters [γ-aminobutyric acid (GABA), serotonin and norepinephrine] and δ-aminolevulinic acid (and therefore in haem synthesis). Dietary sources include meats, whole grains, vegetables and nuts.[67,91,170]

Pyridoxine-5′-β-D-glucoside is the major, naturally occurring form of vitamin B_6. It undergoes hydrolysis in the intestine and is absorbed by diffusion from the lumen of the small intestine. Vitamin B_6 is not stored and cannot be synthesized. Dietary intake therefore provides the metabolic requirements.[170]

Dietary deficiency is rare; however, there is evidence that the requirements are increased in the elderly. Deficiency may result from alcoholism, malabsorption and high-energy states such as dialysis. Medications such as isoniazid, hydralazine, cycloserine, penicillamine, ethanol and theophylline act as pyridoxine antagonists.[3,67]

Vitamin B_6 deficiency usually occurs in association with deficiencies of other water-soluble vitamins. Deficiency can be diagnosed by assessing plasma or erythrocyte pyridoxal-5-phosphate (PLP) levels. Manifestations of deficiency include the following:[67,91,170]

- stomatitis, angular cheilosis, glossitis;
- irritability, depression and confusion, occurring in moderate to severe depletion;
- normochromic, normocytic anaemia that has been reported in severe deficiency;
- abnormal electroencephalograms, convulsions and peripheral neuropathy.

Long-term use with doses exceeding 200 mg per day (in adults) may cause peripheral neuropathies and photosensitivity.[91]

Elevated homocysteine levels are associated with an increased risk of cardiovascular disease. Vitamin B_6 deficiency is associated with elevated homocysteine levels; low levels of vitamin B_6 may be independently associated with CHD.[168,171] In a case–control study, lower levels of folate and vitamin B_6 were associated with an increased risk of atherosclerosis.[161] The Nurses' Health Study found an

inverse association between higher dietary intakes of folate and vitamin B_6 and CHD.[163] There is evidence of a lower risk of breast cancer in women with higher plasma levels of vitamin B_6.[172] In another study, vitamin B_6 supplementation in the elderly resulted in improvement of long-term memory by improving storage of information.[173]

Zinc

Zinc is a divalent trace metal that plays a critical role in protein synthesis. It also serves as a cofactor, catalyst or a part of several enzymes. It is involved in the synthesis of nucleic acids and gene regulation. Zinc is required for the maintenance of genetic stability and gene expression and for controlling differentiation, proliferation, maturation and programmed cell death. It is essential for the maintenance of plasma membrane integrity. It may have antioxidant and antiatherogenic properties.[27,174,175]

Dietary sources of zinc are red meat, seafood, fresh fruit, vegetables and dairy products. During the process of digestion, zinc is released from these dietary sources. It is primarily absorbed in the jejunum. Its absorption is inhibited by phytates present in many staple foods. Metallothionein, present in the gut enterocyte, is responsible for the homeostatic control of zinc absorption. About 90% of the total body zinc stores are in bone and skeletal muscle. It undergoes enterohepatic circulation. Excretion is mainly faecal, with small amounts being excreted in the urine.[27,92,94]

Data available at present are insufficient to determine the frequency of zinc deficiency in the elderly. Deficiency may be seen with poor dietary intake, inflammatory processes, malabsorption, chronic diarrhoea, sickle-cell anaemia, diabetes, cirrhosis of the liver, thiazide diuretics, lung cancer, following thermal injury, in drug addiction and renal injury.[175,176] Low zinc levels seen in inflammatory conditions result from redistribution of zinc, an action mediated by cytokines. Serum and plasma levels of zinc do not correlate with tissue levels and are not reliable indicators.[27,92,94,175,176] Manifestations of deficiency in the elderly may be subtle; they include the following:

- Impaired immune response. Ageing is associated with an altered T-cell response. Zinc has been identified as a potent T-lymphocyte mitogen. Studies have revealed a beneficial effect of zinc supplementation of immune function.[177–181]
- Anorexia resulting from impaired taste and smell. Several mechanisms have been hypothesized to result in anorexia; however, the relationship between zinc status and anorexia still remains unclear.[182]
- Confusion, irritability and restlessness. Acrodermatitis enteropathica (AE) is an autosomal recessive inherited disease. The manifestations of AE are thought to occur secondary to zinc deficiency. Confusion and apathy in affected children respond to zinc supplementation. Also, zinc deficiency induced in humans may be associated with irritability or apathy, which is reversed with zinc supplementation. However, data on the role of zinc deficiency on mental status in the elderly are limited.[92,183]
- Impaired wound healing. Studies have shown impaired wound healing of pilonidal sinuses and venous leg ulcers in patients with low serum zinc levels.[184,185] Current data on zinc supplementation for pressure ulcers are controversial.
- Diarrhoea has been reported in patients who develop severe zinc deficiency during total parenteral nutrition therapy. There have been no randomized studies on zinc supplementation in the elderly with diarrhoea.[92,186]
- Impaired vision. In a study by Keeling *et al.*,[187] adaptation to darkness was impaired in cirrhotics with low neutrophil zinc concentrations.
- Epidermal abnormalities characterized by skin lesions around body orifices and the extremities as seen in AE. In a study of institutionalized patients with skin lesions and low zinc levels, there was no improvement in skin lesions following supplementation with zinc.[188]
- Impaired spermatogenesis and testosterone steroidogenesis resulting in impaired testicular function. In one study, individuals on a zinc-deficient diet developed decreased libido, depressed serum testosterone levels and marked reduction in sperm count. Hydrochlorothiazide-induced sexual dysfunction associated with low zinc levels may respond to zinc supplementation in some individuals.[92,189,190]
- Disruption of vascular endothelium with possible implications for atherosclerosis.[175]

The Health Professionals Follow-up Study found that zinc supplementation, if taken in doses greater than 100 mg daily or for 10 or more years, was associated with increased risk of developing prostate cancer.[191] Zinc toxicity is relatively unusual; however, high dietary intake may cause nausea, vomiting, epigastric pain, lethargy and fatigue. Immune response may be impaired. It can cause hypocupraemia, macrocytosis or neutropenia.[27]

Copper

Copper plays a significant role in several enzymatic pathways. Some of these enzymes include monoamine oxidase, dopamine-β-hydroxylase, cytochrome *c* oxidase, ferroxidase II, superoxide dismutase and lysyl oxidase. Copper plays an important role in iron absorption and mobilization to sites of erythropoiesis. Copper is essential for inactivation of catecholamines, synthesis and cross-linking of collagen and the conversion of dopamine to norepinephrine.[92,192,193]

The various dietary sources for humans are legumes, nuts and meats.[94] A study by Ma and Betts[194] revealed less than recommended intakes of copper by the elderly. Individuals at risk for copper deficiency include patients

with chronic diarrhoea, those on chronic TPN and those on chronic peritoneal dialysis.[94] Deficiency can be seen in individuals on high-dose oral zinc supplementation. Serum copper levels are used to assess copper status. These levels, however, are affected by inflammation and hormonal status. Ceruloplasmin, the copper-binding protein, is an acute phase reactant. Serum copper levels therefore increase during stress and inflammation.[92] Serum copper levels increase with ageing; however, there is no change in the leukocyte copper levels. Advancing age is also associated with an increase in ceruloplasmin.[192]

Dietary copper is absorbed from the upper gastrointestinal tract (from the stomach to the distal small bowel). Bioavailability is affected by dietary fibre and protein content and the ingestion of other minerals such as zinc. Copper undergoes enterohepatic circulation and only small amounts are excreted in the urine. Portal flow delivers histidine-bound and albumin-bound copper to hepatocytes. Release into the systemic circulation is primarily via the specific transporter known as *ceruloplasmin*.[92,193]

The classic manifestations of copper deficiency can be seen in the congenital disorder Menkes syndrome. It is characterized by eating difficulties, hypothermia, seizure activity, 'steel wool' hair, cerebellar ataxia, profound arteriopathy and early death. Copper deficiency may present as follows:[195-198]

- anaemia, leukopenia and neutropenia; anaemia is unresponsive to iron supplementation;
- hypopigmentation;
- immune dysfunction;
- skeletal abnormalities;
- increased cholesterol with atherosclerosis;
- neurological problems such as Alzheimer's disease.

Copper metabolism seems to be conserved with ageing. Although older individuals ingest smaller amounts than younger individuals, they are able to maintain a metabolic balance.[193]

Severe copper toxicity can result in hepatic necrosis, coma, oliguria, renal failure, hypotension and even death. Mild gastrointestinal symptoms such as nausea, vomiting and abdominal pain can occur in less acute and less serious toxic conditions.[94]

Chromium

Chromium, an essential trace element, was first identified as the glucose tolerance factor which corrected hyperglycaemia in rats.[199] Glucose tolerance factor is a combination of chromium and nicotinamide. Chromium functions as a coenzyme and is also a component of metalloenzymes.[200] Low chromium levels may be seen in some diabetic patients and it may have a role in glucose homeostasis.[201,202] Data suggest that chromium may augment the production and binding of insulin to the receptors.[203] Other data suggest that chromium may have a role in elevating high-density lipoprotein (HDL) and lowering overall cholesterol levels).[204]

Dietary sources of chromium include brewer's yeast, cereals, fruits, vegetables, grains and processed meats.[94,192] Chromium is absorbed in the small intestine and its absorption is determined by the total body chromium concentration. Its absorption is enhanced in the presence of zinc and iron deficiency.[94,205] Vitamin C also enhances its absorption. Non-steroidal anti-inflammatory drugs (NSAIDs) and antacids decrease its absorption.[206,207]

Chromium deficiency is seen in individuals on total parenteral nutrition. Tissue chromium levels decline with age and urinary excretion increases.[94,192] Chromium deficiency has been associated with the following:[92]

- glucose intolerance with peripheral insulin resistance;
- altered lipid metabolism;
- neuropathy;
- encephalopathy.

Chromium toxicity has been described in a patient on chromium supplements who presented with renal insufficiency, elevated liver enzymes, anaemia and thrombocytopenia. Discontinuation of the supplement and supportive measures resulted in normalization of all laboratory values within 1 year. Attention to the use of over-the-counter (OTC) nutritional supplements is important, especially in the elderly.[208]

Table 19.5 summarizes the functions of various vitamins and trace metals and the effects of ageing on these micronutrients.

Conclusion

It is important to maintain adequate intake of micronutrients to maintain health. Data suggest that vitamin and mineral deficiencies exist in the elderly; these are exacerbated during hospitalization, hypermetabolic states, alcohol use, liver disease, diuretic use and laxative abuse. Observational data suggest a link between dietary micronutrient intake and health outcomes. However, randomized control trials have not supported the use of vitamin and mineral supplements among well-nourished individuals. Food still remains the best vehicle for nutrient consumption. The elderly are at great risk of toxicity, with a greater potential for drug–nutrient interactions. Other concerns in the elderly include cost and convenience of administration. The use of vitamin and mineral supplements as anti-ageing treatments or as treatments for specific diseases in the elderly is not supported by the currently available scientific data. Education and counselling are important in this age group in order to maintain adequate nutrient intake via methods that are both convenient and affordable.[6,209]

Table 19.5 Micronutrient functions and the effects of ageing on these micronutrients.

Micronutrient	Function	Effect of ageing
Vitamin A	Prevention of xeropthalmia, phototransduction, cellular differentiation and integrity	Intake decreases with ageing, retinol levels correlate poorly with vitamin A status. Hepatic levels appear unchanged
Vitamin D	Calcium and phosphorus homeostasis	Decreased levels of 1,25-dihydroxyvitamin D
Vitamin E	Antioxidant and free-radical scavenger, stabilization of cell membranes	Unknown
Vitamin K	Central role in blood coagulation	Unknown
Vitamin B_1 (thiamine)	Oxidative decarboxylation of α-keto acids and *trans*-ketolase degradation	Decreased thiamine levels
Vitamin B_2 (riboflavin)	Acts with its coenzymes flavin mononucleotide and flavin adenine dinucleotide in oxidation–reduction reactions	Erythrocyte glutathione reductase activity declines with ageing
Vitamin B_3 (niacin)	Dehydrogenase reactions as a coenzyme for nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate	Probably decrease with ageing
Vitamin B_6 (pyridoxine)	Cofactor for intermediary metabolism	Pyridoxal phosphate levels decline
Folate	Single carbon atom transfer in intermediary metabolism	Unknown
Vitamin B_{12} (cobalamin)	Metabolism of fatty acids and methyl transfer	Levels decrease with ageing
Vitamin C (ascorbic acid)	Antioxidant and reduces harmful free radicals. Important for collagen and norepinephrine synthesis	Levels decrease with ageing
Arsenic	Urea cycle, myocardial muscle function and triglyceride synthesis	Unknown
Boron	Bone structure, mineral metabolism	Unknown
Chromium	Glucose homeostasis, lipid metabolism	Decrease
Cobalt	Erythropoiesis and triglyceride synthesis	No change
Copper	Cholesterol metabolism, erythropoiesis, collagen cross-linking, conversion of dopamine to norepinephrine, electron transport chain, coagulation factor V	Increase in serum, decrease in saliva, hair and heart
Fluoride	Bone structure and tooth enamel	Increase up to age 60, then decline in skeleton
Iodine	Thyroid hormones	Increase in serum after age 45
Lead	Uncertain	Unknown
Lithium	Endocrine secretory functions	Unknown
Manganese	Protein and energy metabolism, mucopolysaccharides	No change in serum, reduced in kidney and heart
Molybdenum	Uric acid production, oxidation of sulfite to sulfate	Unknown
Nickel	RNA and DNA structure, membrane stabilization, iron absorption and metabolism, pituitary function	Increase in lungs
Selenium	Constituent of glutathione peroxidase, T and B cell function, muscle metabolism	Decrease
Silicon	Bone and connective tissue structure	Decrease in aorta and skin
Tin	Induces haemoxygenase and carbon monoxide production	Increased in Alzheimer's disease
Vanadium	Cholesterol synthesis, catalysis of oxidation–reduction reactions	Unknown

Key points

- The elderly are at increased risk of undernutrition as a result of multiple factors such as physiological anorexia of ageing, physiological changes affecting digestion, absorption and metabolism of nutrients, social isolation, chronic diseases, sensory impairment, cognitive impairment, depression and polypharmacy.
- There is an overall lack of evidence on the nutritional needs of the elderly, with a particular lack of data from clinical trials.
- Vitamin disorders present atypically or are masked by coexisting diseases or a general failure to thrive.
- Vitamin preparations are consumed on a daily basis by 20–60% of the elderly and drug–nutrient interactions are common in this population because of the high incidence of polypharmacy.
- The use of vitamin and mineral supplements as anti-ageing treatments or as treatments for specific diseases in the elderly is not supported by the currently available scientific data.

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CHAPTER 20

Obesity

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Age-related changes in body composition

At different ages, the same level of body mass index (BMI), calculated as $kg\,m^{-2}$, corresponds to different amounts of fat and fat-free mass. With age, whole-body fat mass (FM) remains relatively stable but increases as a percentage of body weight due to decreased lean mass, whereas both percentage and absolute abdominal fat mass increase. Fat mass peaks at age 60–75 years, whereas muscle mass and strength start to decrease at age 30 years, with accelerated loss occurring after ~60 years of age.[1] In addition, there tends to be a redistribution of fat viscerally and inter- and intra-myocellular fat increases. A number of factors are associated with the age-related changes in body composition. There is a decrease in overall energy expenditure and a significant component of this change relates to decreased physical activity. The decrease in skeletal muscle mass is a consequence of reduced physical activity, increases in pro-inflammatory cytokines (e.g. interleukin-6 and tumour necrosis factor-α) and decreased production or resistance to the actions of anabolic hormones.[1] Visceral obesity, which results in an increase in inflammatory cytokines and a decrease in anabolic hormone levels, is associated with insulin resistance. Intramuscular fat infiltration is associated with both increased insulin resistance and accelerated loss of skeletal muscle strength.[2] Reduced growth hormone and testosterone levels in obese older people have been associated with decreased muscle mass and strength.

Energy expenditure

Age-related decreases in energy expenditure are primarily due to decreased physical activity and reduction in resting metabolic rate (RMR). The decline in RMR with age is not entirely attributable to the reduction in fat-free mass (FFM), as RMR in people aged 60 years and above is lower than that of younger individuals after adjusting for FFM, fat mass and gender. In an 8 year longitudinal study of men and women >60 years of age in Germany, the reduction in RMR per decade was 5% in men and 3% in women after adjusting for body composition, and physical activity energy expenditure also decreased, resulting in a reduction in total energy expenditure per decade of 7.5% in men and 6% in women.[3] In the Baltimore Longitudinal Study of Aging, RMR decreased with age in both men and women independently of BMI, and the rate of decline was faster at age 70–80 than at age 40–50 years.[4]

The thermic effect of food (TEF), which is the increase in energy expenditure in response to macronutrient intake and accounts for up to 10% of total energy expenditure, declines with ageing. The TEF after a glucose load has been found to be ~50% less in healthy men aged 54–75 years than in men aged 19–36 years.[5] Furthermore, TEF was higher in men who habitually exercised than their sedentary counterparts in both age groups.[5] This suggests an additional mechanism by which regular physical activity may prevent obesity in the elderly. Although obese elderly people have lower basal fat oxidation (adjusted for FFM) than younger individuals, 24 h fat oxidation during exercise is higher in normally sedentary older (65 years) men than younger (25 years) men after adjusting for FFM,[6] suggesting that the reduction in nutrient utilization in the obese elderly is largely due to an increase in visceral and intramuscular fat.

Energy intake

Food intake is regulated by a complex system involving orexigenic (appetite-stimulating) and anorexigenic (appetite-inhibiting) hormones that link hypothalamic satiety centres with gastrointestinal function and energy stores (Figure 20.1). Ghrelin, produced in and secreted from the gastric mucosa, is increased by fasting and low-protein diets and inhibited by somatostatin, growth hormone

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

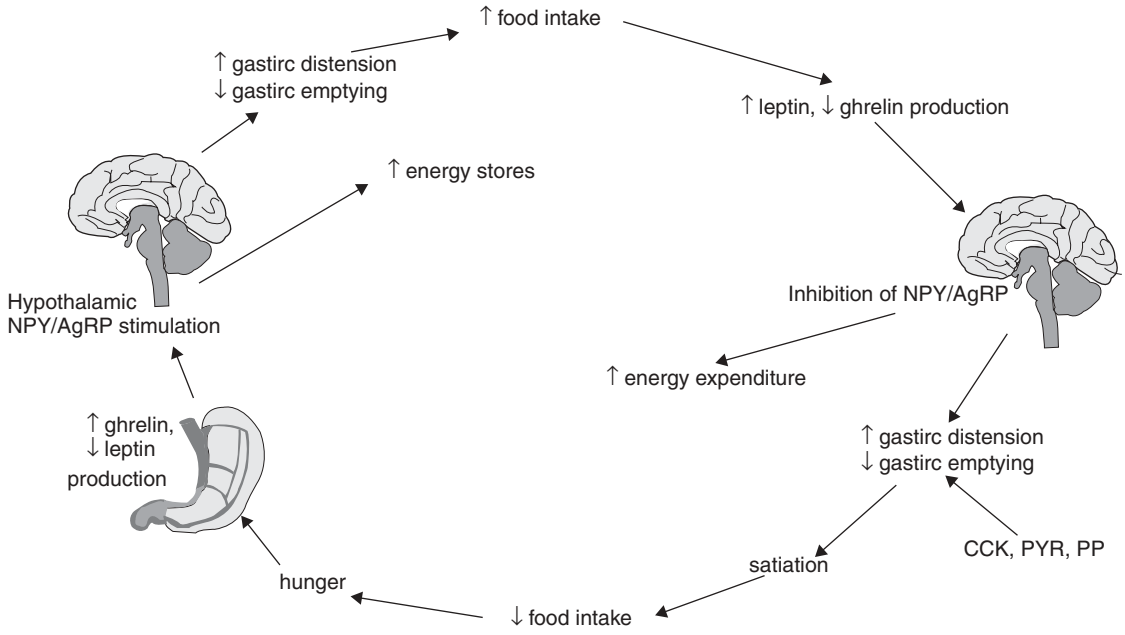

Figure 20.1 Hormonal regulation of energy homeostasis.

and a high-fat diet. Ghrelin is the main orexigenic signal that stimulates neuropeptide Y (NPY) and agouti related peptide (AgRP) in the hypothalamus. NPY and AgRP, which are capable of orexigenic stimuli themselves while simultaneously antagonizing anorexigenic melanocortin pathways, increase appetite, gastric motility and triglyceride stores in adipocytes, but reduce energy expenditure, resulting in net body weight gain. Conversely, the actions of NPY and AgRP are inhibited by the anorexigenic stimulus of leptin, secreted from adipocytes, especially after a meal. Obesity is associated with elevated plasma leptin levels in the elderly, as in younger people.[7] Other gastrointestinal peptides, such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP) and peptide YY (PYY) 3–36, act in synergy with leptin to reduce gastric emptying, resulting in increased gastric distension, which promotes satiety.

There is evidence of altered synthesis and/or secretion and reduced responsiveness to centrally secreted and gut hormones regulating appetite and metabolism in elderly people as compared with young adults; this may contribute to age-related changes in appetite and energy regulation. Compared with younger people, the plasma level of the hormone CCK, which is secreted from the proximal intestine in response to ingestion of fat and protein and induces satiation, is higher in the elderly,[8] but CCK has a weaker than expected effect in limiting meal size in older people.[8] In elderly subjects (mean age 80.7 years), the effect of a carbohydrate-rich test meal to suppress active and total ghrelin levels is limited as compared with younger subjects.[9] Elderly people tend to be less sensitive to satiety cues, follow eating patterns according to habit or schedule and under-report energy intake.[10]

Assessment of obesity with increasing age

Body mass index is of limited utility in assessing obesity in older people due to the age-related changes in body composition. The relationship between BMI and cardiovascular risk and mortality in the elderly is flattened and a high BMI carries a lower risk than in younger people. In contrast, a low BMI, which reflects a low lean body mass, confers a higher risk in older people in comparison with younger people. The combination of a low lean body mass and increased fat mass, known as sarcopenic obesity, confers the highest risk of frailty and death. Sarcopenic obesity increases in prevalence with age and is associated with functional decline, and also other causes of morbidity and mortality in the elderly. Various definitions of sarcopenic obesity have been proposed, such as relative skeletal muscle index (muscle mass divided by height squared) less than two standard deviations below the gender-specific mean of young adults and percentage body fat greater than median (27% in men and 38% in women); or muscle mass in the lower two and fat mass in the upper two quintiles of the population.[1] Depending on the definition used and populations studied, the prevalence varies from 4.4 to 9.6% in men and from 3.0 to 12.4% in women.[1] Identification of sarcopenic obesity requires precise, simultaneous methods of measuring body fat and muscle mass, such as dual-energy X-ray absorptiometry

(DEXA). Bioelectrical impedance analysis (BIA) tends to underestimate fat mass in obese subjects[11] and the reference ranges for the definition of sarcopenic obesity have not been widely validated. Computed tomography (CT) scanning is of greater precision, but is relatively expensive and may be less accessible.

Waist circumference (WC) correlates with abdominal fat mass as measured by CT and has been proposed as an additional measure for the definition of obesity in the elderly.[7] Adults aged 51–72 years with BMI in the normal range (18.5–25 kg m^{-2}) but WC ≥102 cm (men) or ≥88 cm (women) have a 20% higher risk of all-cause mortality than their counterparts with similar BMI but normal WC.[12] Waist:hip ratio (WHR) is an alternative measure that provides some assessment of lean body mass and subcutaneous fat mass. A WHR exceeding 1.0 is associated with increased risk of obesity-related comorbidities, particularly cardiovascular disease. WHR is a better predictor of obesity-associated morbidity and mortality than BMI in the elderly.[12–14]

Prevalence of obesity in older people

The prevalence of obesity (BMI ≥30 kg m^{-2}) in older people has been increasing in the last decade and ranges from ~15–40%, with a slightly higher prevalence in women (Table 20.1). In the United States, the prevalence of obesity (BMI ≥30 kg m^{-2}) in men aged 60 years and above increased significantly from 31.8% in 1999 to 37.1% in 2008 and remained similar in women in the same age group at ~35%.[15] The 2004 Survey of Health, Ageing and Retirement found that the prevalence of obesity in adults aged above 50 in 10 European countries ranged from 12.8 to 20.2% in men and from 12.3 to 25.6% in women.[16] Obesity will continue to be a major problem in ageing populations worldwide.

Consequences of obesity in the elderly

Overall mortality

In contrast to young and middle-aged populations, in which the mortality risk increases with BMI, the relationship between BMI and mortality in the elderly may be U-shaped or reverse J-shaped, with increased mortality risk at BMI exceeding 35 kg m^{-2}. The range of BMI which is associated with the lowest risk of mortality in older adults in most retrospective studies ranged from 27 to 30 kg m^{-2} [7,16] and is 2–5 kg m^{-2} higher in women than men.[7] Several explanations have been proposed for this apparent paradox of overweight elderly having a lower risk of death: overweight people who are more susceptible to the adverse effects of obesity tend to die younger, leaving their peers of similar weight to be included in studies of older subjects; the effects of confounding conditions such as smoking and weight change due to undiagnosed chronic disease are difficult to separate from the effects of obesity *per se*, and older people may succumb to apparently-unrelated comorbidities. The elderly at greatest risk are those who are simultaneously sarcopenic and abdominally obese.

Body composition, in particular increased abdominal adiposity and reduced muscle mass, as measured by large waist circumference and waist:hip ratio, may be a better predictor of cardiovascular and all-cause mortality than high BMI. In the Rotterdam Study, WC ≥102 cm in men and ≥88 cm in women with normal BMI was associated with 20% higher mortality risk compared with subjects with a combination of normal BMI (18.5–<25 kg m^{-2}) and normal waist circumference[12] In a large study of community-dwelling adults aged 75 years and older, increasing WHR was associated with mortality from cardiovascular disease, with WHR exceeding 0.99 conferring the highest risk of mortality in non-smoking men, and WHR >0.90 in non-smoking women was associated with the greatest risk

Table 20.1 Prevalence (%) of overweight and obesity in older persons.[15,16]

Country	Men		Women	
	Overweight: BMI 25.0–29.9 kg m^{-2}	Obese: BMI ≥30.0 kg m^{-2}	Overweight: BMI 25.0–29.9 kg m^{-2}	Obese: BMI ≥30.0 kg m^{-2}
Austria	51.9	18.0	35.4	19.7
Denmark	45.3	13.4	31.0	13.3
France	48.3	15.1	30.1	15.1
Germany	50.9	16.9	37.8	17.4
Greece	54.5	16.8	41.9	21.9
Italy	50.1	15.2	36.4	17.1
The Netherlands	48.5	13.0	36.0	16.5
Spain	49.9	20.2	41.5	26.6
Sweden	47.1	12.8	33.8	14.4
Switzerland	46.6	3.0	29.1	12.3
United States	41.3	37.1	35.0	33.6

of death.[13] In the MacArthur Successful Aging Study, a longitudinal study of high-functioning men and women aged 70–79 years, there was a graded relationship between WHR and all-cause mortality in women (relative risk 1.28 per 0.1 increase in WHR) and a threshold relationship in men (relative risk 1.75 for WHR >1.0 compared with WHR ≤1.0.[14]

Mobility-related disability, functioning and quality of life

Aging is associated with reduced muscle strength and mass and increased prevalence of osteoarthritis (OA), which adversely affects mobility, ability to perform activities of daily living and quality of life. Obesity is associated with increased risk of knee OA, possibly due to mechanical strain on weight-bearing joints, although metabolic syndrome is now recognized to be a risk factor for OA. In a community-based study of people aged 65–80 years, up to 96% of obese (BMI $\geq 30\,kg\,m^{-2}$) subjects were frail, as determined by physical performance test scores, peak oxygen consumption and self-reported ability to perform activities of daily living.[17] The same study also found that obesity was associated with a lower health-related quality of life, as assessed by the SF-36 physical function scoring. Sarcopenic obesity in particular is associated with high risk of impaired mobility and reduced functioning. The combination of obesity and low muscle strength was associated with the development of mobility-related disability in 930 people aged 65 years and above in the InCHIANTI study in Italy.[18] Despite the positive association between weight and bone mineral density, a recent study found that high body weight or BMI increased the risk of vertebral fractures in postmenopausal osteoporotic women.[19] Vitamin D deficiency, which is more prevalent in obese sedentary elderly because of reduced exposure to sunlight, impairment of vitamin D synthesis in the skin with ageing and obesity-associated reduction in bioavailability of cutaneous and nutritional vitamin D, is likely to contribute to osteopenia, fractures, muscle weakness and reduced mobility.

Metabolic syndrome and type 2 diabetes mellitus (T2DM)

The prevalence of the metabolic syndrome (defined by the presence of at least three of the following characteristics: WC >102 cm in men and 88 cm in women, high-density lipoprotein cholesterol $<1\,mmol\,l^{-1}$ in men and $1.3\,mmol\,l^{-1}$ in women, blood pressure >130/85 mmHg, serum glucose $>6.1\,mmol\,l^{-1}$) increases with age. Increased body fatness and increased abdominal obesity, rather than ageing *per se*, are thought to be directly linked to the greatly increased incidence of metabolic syndrome and T2DM among the elderly. As in younger people, increased abdominal fat mass is independently associated with the development of metabolic syndrome in older men and women and waist circumference, a surrogate of abdominal adiposity, is positively correlated with dyslipidaemia, fasting glucose and hypertension, independently of BMI and age. Visceral adiposity-mediated inflammation is involved in the pathogenesis of insulin resistance in elderly obese adults. The age-related reduction in insulin sensitivity is likely to be due to increase in adiposity rather than being a consequence of ageing *per se*.

Fatty liver

Infiltration of the liver with fat (hepatosteatosis) is a feature of the metabolic syndrome and insulin resistance. When inflammation is present, the condition is referred to as steatohepatitis. Progression to cirrhosis may occur, particularly in the presence of chronic viral hepatitis. In the elderly, the prevalence of fatty liver has been reported to be 3.3% in male and 3.8% in female non-obese individuals, compared with 21.6% in male and 18.8% in female obese individuals.[20] As in younger individuals, it is independently related to coronary risk factors in the elderly.

Pulmonary function

Lung function, as measured by height-adjusted forced expiratory volume in 1 s and forced vital capacity on spirometry, decreases with age in elderly men and women. Increase in abdominal fat and reduction in lean body mass are significant predictors of lung function decline, which is greatest in people with both of these factors.[21] Abdominal obesity is also associated with obstructive sleep apnoea, hypoventilation due to reduced respiratory compliance and increased work of breathing caused by increased weight on the chest wall. Older obese men are at highest risk of developing sleep apnoea: a 5% increase in BMI is associated with a 27% increase in respiratory disturbance index (number of apnoeas and hypopnoeas divided by estimated hours of sleep) in 60-year-old obese men.[21]

Hypogonadism

According to a consensus statement from the International Society of Andrology, International Society for the Study of Aging Male, European Association of Urology, European Academy of Andrology and American Society of Andrology, hypogonadism is defined by low libido, erectile dysfunction, decreased muscle mass and strength, increased fat mass, osteopenia, reduced vitality and/or low mood, in association with a morning (7–11 a.m.) serum total testosterone level below $8\,nmol\,l^{-1}$ ($230\,ng\,dl^{-1}$). Plasma testosterone levels fall progressively with age, but are significantly lower in men with visceral obesity, independent

of age. In the Massachusetts Male Aging Study,[22] the Florey Adelaide Male Ageing Study[23] and the European Male Ageing Study,[24] obesity was found to be the single most powerful predictor of low testosterone in ageing men. It is likely that, in addition to the effects of increased visceral fat, a range of health (sleep disorders, type 2 diabetes, depression, medication used), lifestyle (poor diet), environmental and psychosocial factors (stress, loss of a partner), account for the age-related decrease in testosterone. Obstructive sleep apnoea, the severity of which is strongly weight related, is associated with low testosterone levels, and also an increased risk of TDM and CVD.[25] Irrespective of cause, a low testosterone level has been shown to be a risk factor for cardio-metabolic and respiratory disease-related mortality.[25] Insulin resistance, increased aromatization of testosterone to estradiol and pro-inflammatory cytokine production in adipose tissue are likely to contribute to secondary hypogonadism in obese men.

Urological problems

Obesity, especially central adiposity, is a risk factor for both storage and voiding type lower urinary tract symptoms (LUTS) in men and women. In the Boston Area Community Health (BACH) Survey of healthy adults aged 30–79 years, waist circumference was significantly higher in men with more severe LUTS, with 43.2% of men with the most severe symptoms having BMI $\geq$30 kg m^{-2}.[26] Women in the BACH survey who reported the most severe urinary symptoms had average BMI 34.5 kg m^{-2} and the highest waist circumference and prevalence of obesity-related metabolic comorbidities.[27] The pathogenesis of obesity-associated urinary tract dysfunction is likely to be multifactorial, due to a combination of mechanical factors such as prostatic hyperplasia in men and the effects of raised intra-abdominal pressure on urethral structures and the pelvic floor in women, alterations in smooth muscle function in the urinary tract secondary to inflammation, and endothelial dysfunction and hyperactivity of the autonomic nervous system.

Psychological problems

Both obesity and ageing are associated with a higher risk of depression. The Health, Aging and Body Composition Study[28] demonstrated a longitudinal relationship between obesity (BMI) and more particularly visceral obesity (as measured by CT), and the development of depressive symptoms in community-dwelling, well-functioning men aged 70–79 years.

Management of obesity in the elderly

Age-related changes in energy expenditure and body composition, the presence of both obesity- and non-obesity-related comorbidities and limited evidence for the benefits of weight loss complicate the formulation of guidelines for the management of obesity in the elderly. Moreover, pharmacological and surgical interventions that are effective in young adults cannot always be safely and successfully translated into an older population. A recent meta-analysis[29] examined nine randomized controlled trials of weight loss in community-dwelling obese (mean baseline BMI $\geq$30 kg m^{-2}) subjects of mean age at least 60 years, for which follow-up data were available for a minimum of 1 year. Overall, intervention subjects lost an average of ~3 kg compared with controls. The meta-analysis concluded that cholesterol levels were not significantly improved and that there was insufficient evidence for benefits of weight reduction on other cardiovascular risk factors, exercise capacity or quality of life. Another meta-analysis of 16 weight loss trials in subjects aged $\geq$60 years or older with baseline BMI $\geq$27 kg m^{-2}, which included interventions of 6–12 months duration,[30] concluded that weight loss produced clinically important benefits in type 2 diabetes, coronary artery disease and osteoarthritis. The authors included only studies which produced more than 3% or 2 kg weight loss, which may account for the significant improvements seen in glycaemic control and cardiovascular risk.

Diet and physical activity

It is important that specific vitamin deficiencies which may be common, for example, vitamins D and B_{12}, are detected and corrected. Optimization of macronutrient intake will have at least the same and perhaps greater benefits in older than younger individuals. In the obese elderly, moderate degrees of caloric restriction with low saturated fat diets to induce weight loss of 5–10%, in combination with regular physical activity, exert beneficial metabolic effects and stabilize age-related loss of muscle mass. Reducing weight *per se* can improve mobility and quality of life by decreasing the mechanical strain on joints and muscle. In men and women aged at least 65 years with BMI $\geq$30 kg m^{-2}, 10% weight loss induced with a low-fat (<30%) diet with moderate caloric restriction (500–750 kcal per day) and supervised group exercise over 6 months has been shown to produce significant improvements in blood pressure, fasting glucose and triglycerides and inflammatory markers.[31] Moderate caloric restriction and exercise were more effective than exercise alone in reducing weight and fat mass and improving insulin sensitivity in adults aged 65 years and above with mean BMI 34.5 kg m^{-2} and metabolic syndrome.[32] Dietary requirements should also be tailored to comorbidities such as diabetes mellitus, hypertension dyslipidaemia, congestive cardiac failure and renal impairment, which are more prevalent in overweight and obese elderly. Greater degrees of caloric restriction with diets providing less than 800 kcal

per day, which are useful in younger subjects to induce weight loss exceeding 10% in a short period, contribute to loss of lean body mass, dehydration and malnutrition (especially protein, vitamins D and B_{12} and fibre) and hence are best avoided in older patients. Weight loss from caloric restriction alone, without adequate physical activity, may reduce muscle and bone mineral mass in sarcopenic obesity, which compromise mobility without a reduction in cardio-metabolic risk.

Regular physical activity in the elderly reduces the risk of obesity, cardiovascular disease, stroke, hypertension, type 2 diabetes, osteoporosis, breast and colon cancer, anxiety and depression and the risk of falls and disability. The American College of Sports Medicine and the American Heart Association recommend a minimum of 30 min of moderate-intensity aerobic physical activity on 5 days per week or vigorous-intensity aerobic activity for at least 20 min on 3 days per week, and also resistance training for muscle strengthening and flexibility exercises on 2 days per week and balance exercises on 3 days per week.

Most weight loss trials in the elderly utilized exercise training in addition to caloric restriction to achieve weight loss of 5–10%.[29–34]. The Positive Action for Today's Health trial found that at least 45 minutes per week of moderate-intensity exercise for 12 months reduced fat mass, insulin and leptin concentrations in overweight or obese women aged 50–75 years.[33] In the Arthritis, Diet and Activity Promotion Trial, supervised exercise for 1 h on at least 3 days per week in combination with caloric restriction to 500 kcal per day for 18 months in elderly (mean age 69 years) people with BMI $\geq 28\,kg\,m^{-2}$ and knee osteoarthritis produced ~5% reduction in body weight and was associated with improved physical function, decreased knee pain and reduced mortality risk.[34] Assessment for ischaemic heart disease, with or without exercise stress testing, may be necessary in the elderly obese before starting an exercise programme. Regular physical activity that includes a resistance component should be used in conjunction with very modest caloric restriction and optimization of macronutrient content (low saturated fat and refined carbohydrate, adequate fruit and vegetables and whole-grain cereals, low-fat dairy products and sufficient protein from unprocessed meat, fish and chicken) to avoid loss of muscle and bone mass and optimize overall health and function, in all lifestyle modification programmes in obese elderly individuals.

Pharmacotherapy and surgery

Pharmacological treatment of hypercholesterolaemia and hypertension in older people is beneficial in the primary and secondary prevention of cardiovascular morbidity and mortality. Metformin has been shown to delay the progression of glucose intolerance and impaired fasting glycaemia to diabetes even in elderly people. Specific pharmacological and surgical therapy to induce weight loss in the elderly should be considered in the event of failure of dietary intervention and exercise to induce weight loss. Sibutramine, (an inhibitor of norepinephrine and serotonin reuptake) and orlistat (inhibitor of lipase in the gastrointestinal tract), the most extensively studied weight loss medications, are FDA approved for the treatment of obesity and have been found to be effective and safe for weight loss and long-term maintenance in studies comprising mostly young to middle-aged adults. In elderly obese patients, orlistat in combination with a hypocaloric diet produces more weight loss than diet alone, with no significant increase in adverse effects,[35] although deficiencies of fat-soluble vitamins may occur and need to be monitored and there are rare reports of severe liver dysfunction. There is a paucity of efficacy and safety data for other weight loss drugs in older patients. Furthermore, comorbidities, impaired cardiovascular and renal function, polypharmacy and age-related changes in drug metabolism are prevalent in the obese elderly, increasing the risk of adverse effects and interactions with other medications. Sibutramine increases blood pressure and is contraindicated in patients with uncontrolled hypertension, coronary artery disease, stroke and arrhythmias. The safety of phentermine has not been established in the elderly, but it seems likely that it may result in complications similar to sibutramine. In 2010, sibutramine was withdrawn from marketing due to increased risk of cardiovascular events in overweight and obese adults aged 55 and above in the Sibutramine Cardiovascular Outcomes Trial.

Bariatric surgery is recommended for patients with BMI $\geq 40\,kg\,m^{-2}$ without or BMI $\geq 35\,kg\,m^{-2}$ with obesity-related comorbidities who have failed non-surgical attempts at weight reduction.[36] Laparoscopic gastric banding, vertical banded gastroplasty and Roux-en-Y gastric bypass are highly effective in producing weight loss and result in improvement or complete resolution of obesity-related comorbidities. Combined restrictive and malabsorptive procedures such as gastric bypass result in greater and more sustained weight loss than purely restrictive procedures (gastric banding and gastroplasty). Long-term (>2 years) remission of type 2 diabetes, hypertriglyceridaemia, hypercholesterolaemia and obstructive sleep apnoea is achieved in 75–90% of patients after successful surgery[36] and most patients enjoy improvements in mobility, osteoarthritis, cardiovascular disease, asthma, respiratory function, fatty liver disease, psychosocial status and quality of life. However, less than 5% of bariatric surgery procedures have been performed in patients aged >60 years, due to concerns about anaesthetic and operative fitness. In a study of 1339 patients from the University Health System Consortium Clinical Data Base, compared with younger people, elderly patients who underwent bariatric surgery had more comorbidity, longer lengths of stay, more postoperative pulmonary, haemorrhagic and

wound complications and higher in-hospital mortality rates.[37] Nevertheless, this study concluded that bariatric surgery in the elderly was safe because the observed mortality was better than the expected (risk-adjusted) mortality.

Multidisciplinary management of the obese elderly

Obese elderly persons are ideally managed by a multidisciplinary team, consisting of physicians, dieticians, therapists and exercise trainers, psychologists, caregivers and a bariatric surgeon if necessary. Primary care physicians are best placed to initiate weight loss interventions as part of individualized management of obesity and related comorbidities in each patient, involve other members of the multidisciplinary team as appropriate and coordinate the roles of team members (Table 20.2), follow up on weight maintenance and encourage therapeutic lifestyle modification.

Table 20.2 Multidisciplinary management of obesity in older persons.

Physician

- Assess the need for weight loss and readiness of patients to lose weight
- Identify barriers to weight loss, e.g. excessive caloric intake, insufficient physical activity, psychosocial factors
- Counselling on behaviour change, referral to dietician, therapists/trainers and psychologist
- Individualize weight loss targets and monitor efficacy and tolerance of interventions
- Pharmacological treatment if necessary: metformin, orlistat, analgesics for joint and muscle pain, vitamin D supplementation
- Referral for bariatric surgery if lifestyle modification and pharmacological treatment fails and/or severe obesity is unlikely to respond to non-surgical treatment alone
- Continue follow-up and medical management after successful weight loss

Dietician

- Detailed advice on diet modification
- Reinforcement of compliance with diet, e.g. by food diaries, educational media, regular weigh-ins

Physiotherapists, occupational therapists, exercise trainers

- Develop individualized exercise programme to focus on specific areas as required, e.g. mobility, endurance, strength, flexibility
- Advise on home modification and specific equipment to facilitate mobility and safety
- Caregiver training

Psychologist

- Identify and assist in overcoming psychological barriers to behaviour change, e.g. anxiety, depression, poor self-image
- Motivate continuing attempts at weight loss
- Counselling pre- and post-bariatric surgery

Bariatric surgeon

Caregivers in the home, hospital, and long-term care facilities should be involved as much as possible in all aspects of weight management in the obese elderly

Conclusion

Obesity in the elderly is multifactorial, due to age-related changes in activity, caloric intake and energy regulation (Table 20.3). As a result of the increase in fat mass, especially visceral fat and the reduction in lean mass, sarcopenic obesity is more prevalent in the elderly and is associated with increased risk of morbidity and mortality (Table 20.4). The management of obesity is multidisciplinary, focusing on regular and appropriate physical activity with moderation of emphasis on optimization of nutrition rather than simply caloric restriction. and the role of pharmacotherapy remains to be defined, but bariatric surgery has proven utility and may be indicated under extreme circumstances (Table 20.5).

Table 20.3 Mechanisms of obesity in older persons.

1 Reduced energy expenditure
   - Decreased physical activity
   - Decreased resting metabolic rate
   - Changes in nutrient utilization
   - Decreased fat oxidation
2 Lesser degree of decrease in energy intake compared to expenditure
   - Reduced response to satiety cues
   - Fixed timing of meals
3 Age-related changes in body composition
   - Increased fat mass
   - Decreased muscle mass
4 Dysfunctional gut and energy hormone regulation
   - Leptin resistance
   - Lack of ghrelin suppression after food intake

Table 20.4 Consequences of obesity in older persons.

- ↑ Cardiovascular and all-cause mortality
- Impaired physical functioning and mobility, osteoarthritis
- Metabolic syndrome, type 2 diabetes, hypertension, dyslipidaemia
- Hepatic steatosis
- Obstructive sleep apnoea, ↓ lung function
- Hypogonadism in men
- Sexual and urological problems in men and women
- Psychological problems
- ↓ Quality of life

Table 20.5 Management of obesity in older persons.

1	Lifestyle modification
	• Caloric restriction and low fat diet
	• Physical activity: endurance, strength, flexibility, balance training
2	Pharmacological
	• Treatment of metabolic risk factors
	• Orlistat for weight loss in conjunction with diet and exercise
3	Bariatric surgery

Key points

- Obesity in old age involves decreased energy utilization and alterations in caloric intake.
- Sarcopenic obesity is a major functional problem in older persons.
- Physical activity is a key to the management of old age obesity.

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SECTION 2

Gastro Disorders

CHAPTER 21

Changes in gastrointestinal motor and sensory function associated with ageing

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Introduction

This chapter reviews changes in gastrointestinal motor and sensory function associated with healthy ageing, together with what is known about the underlying causes and their clinical significance. Illnesses with gastrointestinal complications that are common in the elderly are also discussed, along with medications that potentially affect gastrointestinal motility. The focus is on the oesophagus, stomach and small intestine, since the oropharynx (Chapter 59, Communication disorders and dysphagia), gallbladder (Chapter 23, Liver and gallbladder) and colon and anorectum (Chapter 24, Sphincter function, and Chapter 25, Constipation) are dealt with elsewhere, as are mucosal functions of secretion and absorption.

Control of gastrointestinal motility and sensation

Patterns of motor activity, involving the circular and longitudinal layers of smooth muscle that extend throughout the length of the gut, are coordinated by plexuses of nerves within the gut wall known collectively as the enteric nervous system. Located in the submucosa (submucous plexus) and between the muscle layers (myenteric plexus), this network contains an equivalent number of neurons (about 100 million) to that present in the spinal cord.[1] The intrinsic sensory neurons, interneurons and motor neurons that comprise the enteric nervous system control basic contractile activity such as reflex responses to distension. However, these intrinsic patterns of gut motility are modulated by both extrinsic neural and humoral signals. Central modulation of gut motility occurs via extrinsic sympathetic and parasympathetic nerves, while gut sensation is conveyed to higher centres by both the vagus and spinal afferent nerves, with noxious signals transmitted predominantly via the latter. Descending pathways to the spinal cord modulate the transmission of sensory signals.

Pathophysiology of the ageing gut

In rodent models of ageing, there is a substantial reduction in the number of neurons in the enteric nervous system, which becomes increasingly prominent more distally in the gut (40% loss in the small intestine and 60% in the colon, in the myenteric plexus of rats).[2] Similar neuronal loss is reported in the oesophagus in older humans, while in the human colon the decline in neuron numbers begins as early as the fourth year, but is most marked between young adulthood and old age.[3] Losses are selective for cholinergic neurons and involve both the myenteric plexus (involved with initiation and control of smooth muscle contraction) and the submucous plexus (involved in secretion and absorption and also motor control).[4,5] Nitrergic neurons, which generally mediate inhibitory motor responses, are protected in number but develop axonal swelling and glial cells are also lost in parallel with neurons. Regarding the extrinsic nerve supply to the gut, the number of vagal fibres innervating the upper gastrointestinal tract does not appear to decline in ageing rats, but afferent and efferent fibres undergo morphological changes.[4] In particular, vagal afferents associated with both the muscle wall and the mucosa of the gut degenerate with age, potentially compromising both sensory feedback and gut reflexes.[6] The underlying causes of neuronal loss with ageing remains unclear, although caloric restriction appears to be protective.[7] Recent data also indicate a loss of interstitial cells of Cajal in the ageing human colon;[7] these specialized cells are responsible for the propagation of the electrical rhythm of the gut on which muscle contraction is superimposed. Limitations to our understanding of the pathophysiology of the ageing gut include a relative lack

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of studies relating to the upper gut and the sphincters and the paucity of human data compared with animal models.

The relatively good preservation of gastrointestinal motility in the healthy elderly may imply that the large number of neurons in the enteric nervous system provides a considerable functional reserve, but even this may be limited; transit of a radiolabelled meal through the upper gut occurs at a comparable rate in the healthy elderly and the young, but is slower through the colon in the elderly, where the loss of enteric neurons is greatest.[8] It may therefore not be surprising that constipation is the one gastrointestinal complaint that clearly stands out in the elderly compared with the middle aged.[7] In the oesophagus, selective loss of intrinsic sensory neurons could explain why contractile activity in response to distension (so-called 'secondary peristalsis') occurs less frequently in the healthy elderly than the young.

In contrast to motor function, gut sensation is more consistently impaired with age, as reflected by decreased perception of balloon distension in the oesophagus,[9] stomach[10] and rectum[11] in comparison with young subjects. A selective loss of intrinsic sensory enteric neurons may be responsible. However, the amplitude of cortical evoked potentials recorded from scalp electrodes during repeated oesophageal distension in older subjects is lower than in the young, raising the possibility that altered central processing of signals might also contribute to diminished sensation.[12] In addition to mechanical stimuli, perception of chemical stimuli such as acid decreases with age, suggesting a generalized impairment of gut sensation.

Oesophagus

Patients with disordered oesophageal function can present with dysphagia or 'heartburn' or less specific symptoms such as chest pain or chronic cough. Age-related changes in oesophageal motility are extensively documented, but probably impact mainly on the very old. Classic oesophageal motility disorders such as achalasia, although uncommon, can present particular challenges in the elderly. Gastro-oesophageal reflux disease (GORD) is as prevalent as in the young, often presents atypically and is more likely to be severe.

Changes in oesophageal motor function related to ageing

The oesophagus incorporates striated muscle in the upper portion and smooth muscle in the lower, with an upper oesophageal sphincter (UOS) and lower oesophageal sphincter (LOS) at either end. The term 'primary peristalsis' refers to the coordinated sequence of contraction associated with swallowing, propagated from proximal to distal oesophagus. The LOS relaxes early in this sequence to allow the swallowed bolus to enter the stomach. 'Secondary peristalsis' is triggered by reflux of gastric contents into the oesophagus or experimentally by balloon distension and serves to clear the oesophagus of acid and bile. 'Tertiary contractions' represent spontaneous, uncoordinated oesophageal motor activity. While both tonic contraction of the LOS and its position within the diaphragmatic hiatus are important barriers against acid reflux, transient sphincter relaxations, particularly after a meal, are the most prevalent mechanism of acid reflux in most GORD patients. Defences against reflux include neutralization of acid by saliva (which contains bicarbonate), together with acid clearance by primary and secondary peristalsis.

Oesophageal motility may be evaluated by manometry. In this procedure, a catheter incorporating multiple lumens within a relatively small external diameter is passed through the nose or mouth and perfused with water. Each lumen terminates in a sidehole at a different level of the oesophagus and, when coupled to pressure transducers and displayed as recordings of pressure over time, the assembly provides information about the amplitude, duration and propagation of pressure waves (Figure 21.1). Incorporation of either a sleeve sensor or multiple closely spaced sideholes into the assembly is ideal for measurement of both the resting pressure and

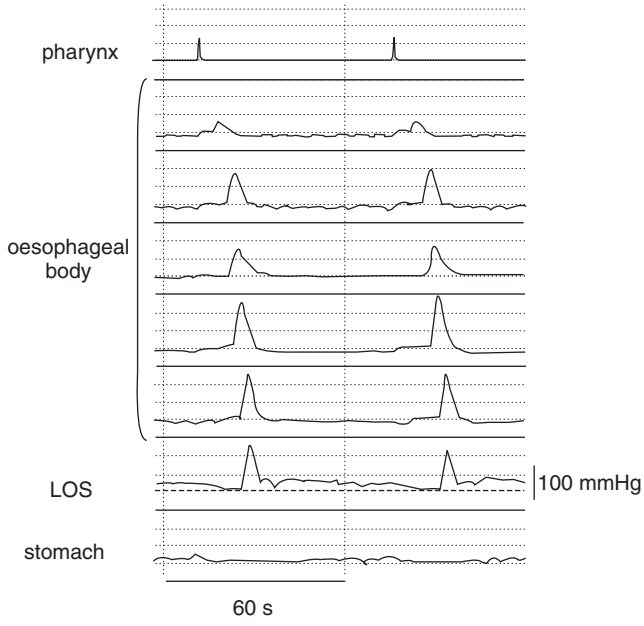

Figure 21.1 Normal oesophageal manometry recording during water swallows, showing primary peristalsis. The pharyngeal pressure wave indicates the onset of swallowing, which is followed by an orderly sequence of waves from one channel to the next. Note the swallow-induced relaxations of the LOS, whose pressure decreases to approximate intragastric pressure (dashed line).

relaxation of the UOS and LOS. Solid-state transducers, mounted at intervals along a catheter, represent an alternative method of manometry to water-perfused catheters. Multi-channel intraluminal impedance, a technique that records electrical impedance between sequential pairs of electrodes, is emerging as a method of evaluating flow of liquid and air in the oesophagus. While offering new insights into oesophageal function, it has yet to be applied specifically to the elderly. Radiographic imaging of swallowed contrast agent can reveal abnormal oesophageal wall movements (especially cineradiography), dilatation or delayed oesophageal transit. Transit can also be evaluated by the passage of a radiolabelled bolus, imaged by a gamma camera – a technique known as scintigraphy. While endoscopy is most useful in demonstrating mucosal lesions or strictures, it may also provide evidence of abnormal motor activity in disorders such as oesophageal spasm or achalasia.

The effects of ageing have been studied more extensively in the oesophagus than any other gastrointestinal region, reflecting both its accessibility and the importance of swallowing disorders in the elderly. Soergel *et al*. coined the term 'prebyoesophagus' in 1964 when reporting radiological and manometric observations in a group of nonagenerians.[13] Only two of 15 subjects had 'normal' oesophageal motility and on barium examination there was a high prevalence of tertiary contractions, delayed clearance and oesophageal dilatation. Manometry showed non-peristaltic, multi-peaked pressure waves. These subjects, however, could scarcely be described as healthy elderly, given the high prevalence of dementia and other chronic illnesses, including diabetes. Not surprisingly, more recent studies indicate that the prevalence and severity of oesophageal motor dysfunction in healthy ageing is less than suggested by early reports.[14] While there are other reports of oesophageal dysmotility in the very old,[15] in subjects aged less than 80 years there appears to be little difference in primary peristalsis when compared with young people, although simultaneous contractions may occur more frequently. The impact of ageing on the amplitude of oesophageal pressure waves may vary by site; distal oesophageal amplitudes increase with age, while a decrease is reported more proximally. Nevertheless, the magnitude of these changes is modest.[16] Secondary peristalsis is elicited less consistently by distending stimuli in the healthy elderly compared with the young[17] and increasing oesophageal stiffness, together with an increased threshold for perceiving distension, may contribute to this phenomenon.[18] In fact, changes in biomechanical properties and primary and secondary peristalsis are observed from as early as 40 years of age.[19]

In the healthy elderly, while both the length of the UOS high pressure zone and its resting pressure are less than in young subjects, relaxation and opening of this sphincter are delayed.[20] The result is a prolongation of the oropharyngeal phase of swallowing and an increase in intra-bolus pressure in the hypopharynx. Although not clinically significant in the healthy elderly, these findings must be taken into account when evaluating swallowing studies in older patients with oropharyngeal dysphagia, where the use of reference ranges derived from the young would be inappropriate. Reflex responses of the UOS to oesophageal stimuli (increased pressure with oesophageal balloon distension and decreased pressure with air distension) appear to remain intact with healthy ageing, but reflex UOS contraction in response to laryngeal stimulation is impaired;[21] the latter could predispose to aspiration. The fact that only the frequency and not the magnitude of the response is diminished suggests that the sensory side of the reflex arc is impaired.

The elderly have an increased prevalence of hiatus hernia (around 60% of those aged over 60 years)[22] and both the resting pressure and intra-abdominal length of the LOS decline with age, while acid exposure increases,[23] implying a predisposition to GORD. Other predisposing factors include reduced flow of saliva and impaired acid clearance. The frequency of transient LOS relaxations, the major mechanism of acid reflux in most individuals, has not been specifically studied in the elderly, nor have mucosal repair mechanisms been compared with the young. The number of reflux episodes appears similar in both age groups, but their duration appears to be more prolonged in the elderly;[24] this may relate to impaired clearance mechanisms. The refluxate may be less acidic due to a higher prevalence of atrophic gastritis in the elderly, but it should be recognized that its bile content may be important in mucosal injury (e.g. Barrett's mucosa) and this has not been studied specifically in relation to age.[14]

Clinical presentation of disordered oesophageal motility

Disordered oesophageal motor function may present with symptoms of difficulty in swallowing (dysphagia) or chest pain. In both nursing homes (50–60%) and general medical wards (10–30%), there is a high prevalence of dysphagia when patients are specifically questioned,[25] although less than half of elderly subjects who reported dysphagia in a population-based survey had consulted a physician about the problem. Potential consequences of dysphagia include aspiration, which contributes substantially to mortality and inadequate intake of nutrition.

Swallowing disorders can be classified into those of oropharyngeal (difficulty initiating a swallow) or oesophageal (impaired transport of swallowed material) origin and these can usually be distinguished with a careful history and examination. The oropharyngeal component of swallowing comprises preparatory (chewing

Table 21.1 Oesophageal causes of dysphagia.

Structural lesions
• Neoplasm
• Peptic stricture
• Rings and webs
• Vascular compression
• 'Pill' oesophagitis
• Reflux oesophagitis
• Eosinophilic oesophagitis
• Diverticula
Motility disorders
• Achalasia
• Diffuse spasm and 'nutcracker' oesophagus
• Non-specific motility disorders
• Systemic disease (diabetes mellitus, progressive systemic sclerosis, Parkinson's disease)

food, mixing with saliva and bolus formation), oral (propulsion of the bolus by the tongue and palate to the pharynx) and pharyngeal (transport through the UOS while protecting the airway) phases. A comprehensive discussion of dysphagia of oropharyngeal origin is included in Chapter 59, Communication disorders and dysphagia.

Potential causes of oesophageal dysphagia are listed in Table 21.1. Key points in the history include whether dysphagia is for solids or liquids, is intermittent or progressive and whether there are associated reflux symptoms such as heartburn.[26] Progressive difficulty in swallowing solids is suggestive of a structural lesion, while dysphagia for both liquids and solids is associated with motility disorders. Endoscopy provides a means to visualize and biopsy structural lesions and may be therapeutic (e.g., dilatation of a peptic stricture). Endoscopy and biopsy are also likely to be helpful when odynophagia (painful swallowing) is the presenting complaint and in the patient with dysphagia can help exclude eosinophilic oesophagitis, which is increasingly being recognized even in older patients.[27] Barium videofluoroscopy provides complementary information regarding motor function and also structural lesions, and manometry is of greatest use in confirming or excluding a diagnosis of achalasia.

Of the primary oesophageal motility disorders, achalasia, diffuse spasm and nutcracker oesophagus are diagnosed over a wide age range. Although the peak incidence of achalasia is in early to mid-adulthood, a second, smaller peak occurs in the elderly.[16] Oesophageal spasm is more commonly diagnosed in people over 50 years of age, whereas non-specific motility disorders are particularly associated with an older population. However, the range of manometric diagnoses in the very old (age 80–93 years) presenting to a clinical motility unit with dysphagia was reported to be broadly similar to that in younger patients.[28]

Achalasia

Achalasia is an oesophageal motor disorder of unknown aetiology, associated with incomplete or absent swallow-induced LOS relaxation and absence of peristalsis in the oesophageal body. Occasionally, simultaneous oesophageal pressure waves of large amplitude are observed (so-called 'vigorous' achalasia). Inflammation of the myenteric plexus is an early histological finding, followed by ganglion loss and neural fibrosis. The condition typically presents with dysphagia for both liquids and solids, although weight loss, regurgitation and aspiration may also be presenting symptoms, particularly in the elderly. Conversely, chest pain is reported less often than in young patients.

A barium swallow may show impaired peristalsis, delayed emptying and dilatation of the oesophageal body (the latter more characteristic in the elderly than the young), with 'bird's beak' or 'rat's tail' tapering at the LOS (Figure 21.2). At manometry, the resting

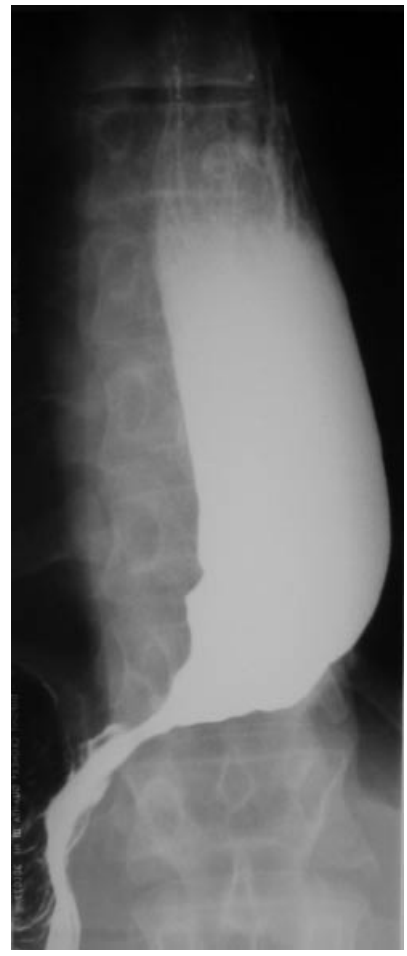

Figure 21.2 Barium swallow in a patient with achalasia, demonstrating a dilated oesophagus with tapering at the distal end.

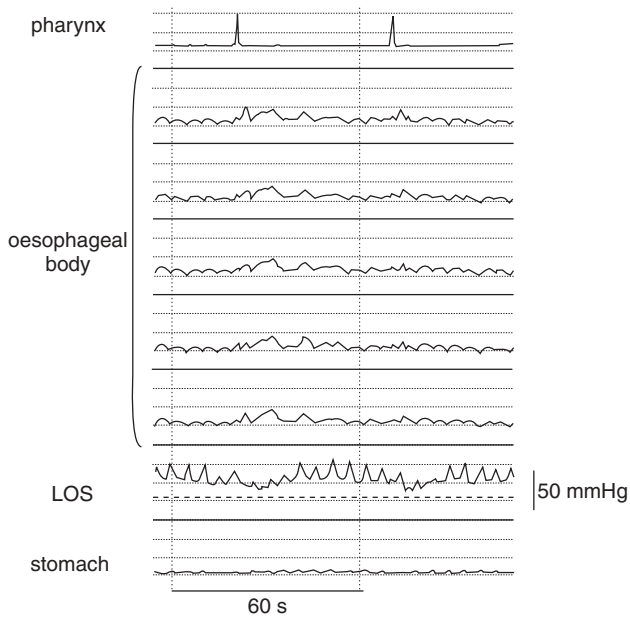

Figure 21.3 Oesophageal manometry in achalasia. Note the simultaneous, small-amplitude pressure waves in the oesophageal body and minimal relaxation of the LOS on swallowing.

LOS pressure may be high or within the normal range, but LOS relaxation on swallowing is either absent or incomplete. In the oesophageal body, pressure waves are simultaneous and of small amplitude or absent altogether (Figure 21.3). Endoscopy (and sometimes endoluminal ultrasound or computed tomography) must be performed to exclude 'pseudo-achalasia', especially in the elderly; this entity presents with features of achalasia, but is due to carcinoma of the distal oesophagus or cardia. A short history of symptoms and disproportionate weight loss are particularly suggestive of the diagnosis.

Pneumatic dilatation and surgical myotomy (now usually performed laparoscopically) represent the most efficacious treatments for achalasia. Relief of dysphagia after surgery appears as good for older as for younger patients (about 80%),[29] while older patients my get better relief from pneumatic dilatation than the young.[30] Oesophageal emptying is improved in a smaller percentage and neither therapy addresses aperistalsis of the oesophageal body. Pneumatic dilatation produces controlled tearing of the LOS and is associated with a risk of oesophageal perforation (about 3%) and induction of reflux symptoms (about 10%). Not infrequently, repeat dilatations are required, although two-thirds had no need for further dilatation in a recent report where an initial series of dilatations was guided by their effect on LOS pressures.[31] While myotomy may be associated with a greater risk of GORD, it can be combined with an anti-reflux procedure. The lower morbidity of dilatation may favour this procedure over surgery in older patients, with the caveat that a thoracotomy is required if perforation occurs. Pneumatic dilatation is more cost-effective than surgical myotomy.

Endoscopic injection of botulinum toxin into the LOS represents an alternative and safe therapy, but adequate symptom relief may be achieved in fewer patients (around 60%)[32] and the benefit lasts around 6 months, so that repeated treatments may be necessary. Therefore, this therapy is best reserved for patients in whom comorbidities represent contraindications to surgery or pneumatic dilatation; this group typically includes the frail elderly. This must be counterbalanced by evidence that the response to both pneumatic dilatation and botulinum toxin is better in older than younger patients. The cost of botulinum toxin injection is slightly greater than that of pneumatic dilatation, but substantially less than that of surgery.

Pharmacological therapy to reduce LOS pressure (nitrates, calcium channel antagonists or sildenafil) is of limited efficacy (possibly even less in the elderly than the young), requires frequent dosing and is associated with side effects.

Patients with achalasia have an increased risk (estimated as 16-fold) of squamous cell carcinoma of the oesophagus, but the absolute risk is small and surveillance endoscopy has not been advocated.[33] Occasional patients have persistent dysphagia despite therapy, together with a tortuous, dilated oesophagus that empties poorly; in these circumstances, oesophagectomy may be required.

Diffuse oesophageal spasm and 'nutcracker oesophagus'

These disorders are diagnosed in a minority of patients with dysphagia or chest pain and in many cases the relationship between symptoms and motor abnormalities is unclear. Criteria for the diagnosis of diffuse oesophageal spasm are inconsistent; the presence of simultaneous oesophageal pressure waves in more than 10%, but fewer than 100% of wet swallows, regardless of amplitude, is a reasonable definition[34] (Figure 21.4). The barium swallow may show segmentation of contrast by contractions or a 'corkscrew' appearance (Figure 21.5). Similar manometric abnormalities may occur in association with diabetes mellitus, alcohol abuse, amyloidosis, progressive systemic sclerosis and GORD. 'Nutcracker oesophagus' is characterized by large-amplitude oesophageal pressure waves, but peristalsis is maintained. The management of both diffuse spasm and nutcracker oesophagus is discussed below, in relation to non-cardiac chest pain.

Non-specific oesophageal motility disorders

Many patients referred for investigation of symptoms such as dysphagia or chest pain have manometric features that

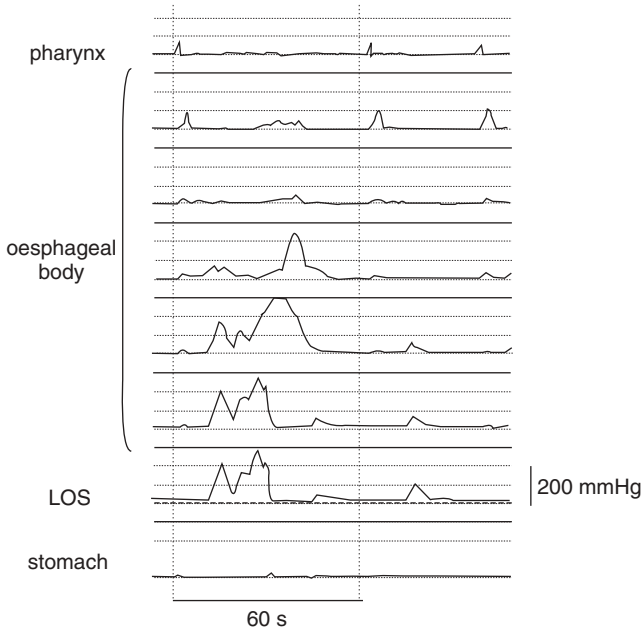

Figure 21.4 Manometry recording in diffuse oesophageal spasm. Note the simultaneous pressure waves after water swallows, including multi-peaked and large-amplitude waveforms.

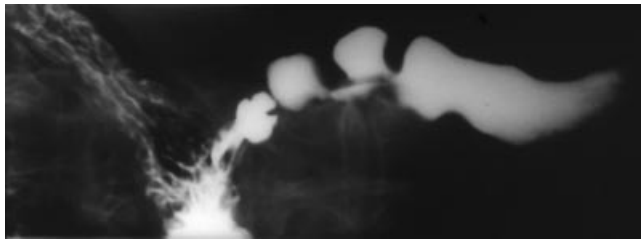

Figure 21.5 Barium swallow in a patient with diffuse oesophageal spasm, demonstrating segmentation of the barium column by contractions, producing a 'corkscrew' appearance.

are outside the normal range, but do not meet formal criteria for the diagnosis of disorders such as achalasia and diffuse spasm. In cases where peristaltic waves are of abnormally small amplitude, absent or fail to traverse the whole oesophagus, often associated with a low LOS pressure, a category of 'ineffective oesophageal motility' has been proposed.[35] Non-specific abnormalities of oesophageal motor function are evident in more than one-third of presentations with dysphagia in patients aged over 65 years, in contrast to the young, where a specific diagnosis can usually be made. It is important to recognize that a causal association cannot be assumed, since the presence of radiographic or manometric abnormalities of oesophageal function correlates poorly with symptoms. Moreover, no specific therapy is available. Symptomatic management includes acid suppression when GORD is a feature and optimizing nutrition.

'Pill oesophagitis'

An important cause of dysphagia or odynophagia in older individuals is mucosal injury caused by impaction of medications in the oesophagus, the incidence of which is likely to be increasing as the number of medications prescribed in this group escalates. Risk factors which are more prevalent in the elderly include less saliva, delayed oesophageal transit and immobility. Capsules may present a greater risk than tablets, due to slower oesophageal transit. The most frequent sites of hold-up are the upper and mid-oesophagus, corresponding to extrinsic compression from left main bronchus, aortic arch or enlarged left atrium and also to a zone of small-amplitude pressure waves between the proximal and distal oesophagus. Numerous medications are associated with oesophageal injury, including potassium chloride, tetracyclines, aspirin, non-steroidal drugs, quinidine, theophylline, ferrous sulfate and alendronate.[36]

Symptoms usually resolve when the offending drug is withdrawn, but may sometimes be persistent and related to stricture formation. Perforation and bleeding are other complications, associated particularly with potassium chloride, quinidine and non-steroidal drugs. The typical endoscopic or barium swallow appearance in pill oesophagitis is of small superficial ulcers. There is anecdotal evidence that sucralfate is beneficial in severe or persistent disease. As a preventive measure, patients should be advised to take oral medications in the upright position, followed immediately by a full glass of water.

Non-cardiac chest pain

Chest pain is a prevalent symptom in the community and not infrequently presents a diagnostic difficulty, especially in older patients who are at greater risk of ischaemic heart disease than the young. The oesophagus is often implicated when cardiac causes have been excluded, but musculoskeletal, pulmonary, pericardial, gastric and biliary pathology should also be considered and an association with panic disorder has been reported.[37]

GORD may be responsible for a proportion of non-cardiac chest pain (NCCP) and about 50% of NCCP patients have excessive oesophageal acid exposure on pH studies. Many patients with excessive acid exposure do not have reflux oesophagitis, which limits the value of endoscopic examination. Rather, a trial of double-dose proton pump inhibitor (PPI) for 2–8 weeks (depending on symptom frequency) is a useful and cost-effective initial test in NCCP, with a sensitivity and specificity as high as 80% each for a diagnosis of GORD. If symptoms are relieved, the dose of medication can subsequently be titrated down to the minimum effective dose. If PPIs are ineffective, then oesophageal manometry and ambulatory pH measurement (while remaining on the PPI) are indicated; the former is

particularly helpful for excluding achalasia. Endoscopy should be performed whenever there are 'alarm symptoms' such as dysphagia, anorexia, weight loss, haematemesis or anaemia. The threshold for endoscopy in older patients should be lower than in the young (age less than 40 years).

The association between NCCP and oesophageal motility disorders, including diffuse oesophageal spasm and 'nutcracker oesophagus', is less strong than previously assumed and even when these disorders are demonstrated, a causal relationship can be difficult to establish, even with 24 h ambulatory manometry.[38] Furthermore, medical therapy for oesophageal motility disorders with smooth muscle relaxants such as nitrates, calcium channel antagonists or sildenafil has limited efficacy and surgical myotomy has had only anecdotal success.

Visceral hypersensitivity is now thought to play a major role in non-GORD-related NCCP and pain-modifying agents, such as tricyclic antidepressants or selective serotonin reuptake inhibitors, have been shown to be superior to placebo in the management of this disorder. Limited data also suggest that theophylline, an adenosine receptor antagonist, may be beneficial. Caution should be exercised in the elderly due to potential side effects of all these agents, particularly when prescribing tricyclics.

Many studies indicate that NCCP, although often persisting over a number of years, has an excellent prognosis in terms of mortality, although the latter point is controversial[39] and may depend on the population from which those with NCCP are drawn.

Gastro-oesophageal reflux disease (GORD)

GORD presents in the elderly with more severe disease (erosive oesophagitis, stricture or Barrett's oesophagus) than in the young,[40] perhaps related to the predisposing factors discussed earlier or to a longer duration of disease.[22] Conversely, symptoms are characteristically milder or may be qualitatively different in the elderly, so that dysphagia, vomiting, respiratory difficulty, weight loss or anaemia are not uncommon presenting features, while 'typical' reflux symptoms such as heartburn occur less often than in the young[41] – the latter perhaps as a result of diminished oesophageal sensitivity. In the general population, symptoms of heartburn or regurgitation have a high sensitivity (about 70%) for a diagnosis of GORD, but a low specificity, when using 24 h pH monitoring as the 'gold standard'; corresponding data are not available for an ageing population. The 'alarm symptoms' mentioned for NCCP are indications for prompt endoscopic investigation.

Atypical or 'extra-oesophageal' manifestations of GORD include chronic cough and asthma and may be mediated either directly by acid–pepsin reflux or by oesophageal acid exposure triggering vagal reflexes. The prevalence of excessive acid reflux in patients complaining of these symptoms is controversial and, as for NCCP, the most useful diagnostic test may be a therapeutic trial of intense acid suppression with double-dose PPI for 2–8 weeks, depending on symptom frequency.

There appear to be no significant differences in the capacity to heal oesophagitis in older patients when compared with the young and PPIs maintain their superiority over histamine receptor antagonists in this age group. No dosage adjustment is needed in the elderly to compensate for age-related changes in renal or hepatic function, but downward titration of the dose according to symptoms may be less appropriate than in the young, especially when the original symptoms were mild or in the setting of complicated GORD. Indeed, continued therapy with a PPI seems markedly to reduce relapse of oesophagitis, compared with stopping therapy after an initial 6 months of treatment.[42] Long-term use of PPIs has generally been regarded as safe; reports of an increased risk of osteoporotic hip fracture[43] have not subsequently been substantiated,[44] although there may be a greater risk (about 1.5-fold) of community-acquired pneumonia,[45] while *Clostridium difficile* infection,[46] malabsorption of vitamin B_{12}[47] and interstitial nephritis also represent potential adverse effects. Concerns about an increased risk of gastric or colon cancer have not been substantiated.[48] Long-term acid suppression in individuals with *Helicobacter pylori* is associated with an increased prevalence of atrophic gastritis, which is thought to be a risk factor for gastric cancer. Therefore, *H. pylori* eradication is generally recommended in patients on long-term PPI therapy, but this is unlikely to be of significance in the very old. Cisapride was commonly used to treat GORD prior to its withdrawal from the market, but there is no good evidence to support the use of currently available prokinetic drugs for GORD in general[49] and there is no information specific to the elderly. Maintenance therapy for GORD has not been specifically compared between elderly and young patients, but long-term medical therapy is likely to be more cost-effective than anti-reflux surgery in older patients, on the basis of the number of years of medical therapy likely to be needed. Nevertheless, the healthy elderly have outcomes from laparoscopic fundoplication that are comparable to the young,[22] with an equivalent safety profile.[50,51] Endoscopic anti-reflux procedures to date have not fulfilled their initial promise and their use should be restricted to clinical trials.

Stomach and duodenum

Although only a modest delay in gastric emptying is observed with healthy ageing, both the perception of gastric distension and humoral responses to duodenal nutrient exposure differ markedly from the young and could contribute to the 'anorexia of ageing'. Moreover, postprandial hypotension, a common cause of falls and syncope in the elderly, can be regarded as a gastrointestinal disorder and

can be related to both the rate of gastric emptying and the small intestinal response to ingested nutrient.

Changes in gastric motor function related to ageing

The stomach is responsible for the accommodation of ingested food and fluids, their mixing with digestive enzymes and grinding of solids into small particles.[52] Gastric emptying reflects the coordinated motor activity of the stomach and duodenum, which is controlled by feedback from neural and humoral signals generated by the interaction of nutrients with the small intestine. As a result of this, the rate of energy delivery to the small intestine is relatively constant and independent of the ingested nutrient load. Small intestinal feedback may be modulated by previous patterns of nutrient intake, so that gastric emptying is retarded in starvation, while emptying of glucose is more rapid after dietary glucose supplementation. The proximal region of the stomach, comprising the fundus and much of the gastric body, relaxes after meal ingestion and acts as a reservoir for the solid component of the meal, while liquids begin to empty. Tonic contraction of the proximal stomach also generates a pressure gradient to assist gastric emptying. The distal stomach, comprising the antrum and pylorus, is responsible for grinding solids and for generating flow across the pylorus – the latter is predominantly pulsatile, rather than continuous. Contractions of the stomach are linked to an underlying electrical rhythm of about three cycles per minute, generated by a gastric pacemaker.

Scintigraphy remains the 'gold standard' for measurement of gastric emptying and the use of dual isotopes allows both the solid and liquid components of a meal to be studied (Figure 21.6).[53] Regional meal distribution can also be evaluated by defining regions of interest within the stomach. Ultrasonography and ^{13}C isotope breath tests are alternative methods of measuring gastric emptying, although the former is restricted to liquid meals. Manometry is used predominantly for research purposes to record the frequency, amplitude and organization of lumen-occlusive contractions in the antrum, pylorus and duodenum. Proximal gastric relaxation in response to a meal can be evaluated in the laboratory using an electronic barostat; the volume of air required to maintain a fixed pressure in an intragastric bag is used as an index of proximal gastric tone. The electrical rhythm of the stomach may be recorded from cutaneous electrodes, although the clinical significance of abnormalities of this electrogastrogram (EGG) is unclear, since they are not specific for particular gastrointestinal disorders.

Healthy ageing appears to be associated with modest slowing of gastric emptying of both solids and nutrient-containing liquids, but the rate of emptying generally remains within the normal range for young subjects.[54,55]

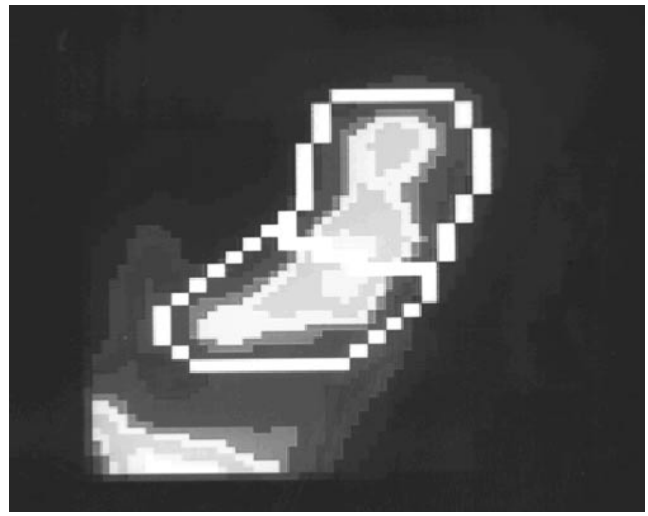

Figure 21.6 Scintigraphic gastric emptying study. Part of the radiolabelled meal is evident in the stomach, while some has emptied into the small intestine (bottom left). Proximal and distal gastric 'regions of interest' are outlined.

The relative slowing of gastric emptying may have implications for appetite regulation, potentially contributing to the 'anorexia of ageing'; prolongation of gastric distension and of exposure of the small intestine to nutrients might lengthen the period of postprandial satiation. Slow gastric emptying, and also alterations in gastric pH (for example, higher pH postprandially than in the young) could also influence the absorption of orally administered medications[56] and a slight reduction in paracetamol absorption has been reported in the healthy elderly compared with the young. However, absorption of benzodiazepines, tetracycline or L-dopa is not significantly altered with age *per se*. A number of systemic disorders, which occur frequently in the elderly, are associated with markedly delayed gastric emptying or gastroparesis (Table 21.2) – acute gastroparesis may also result from the administration of a number of drugs (Table 21.3).

There is little information about the effects of ageing on the mechanics of the stomach, but fasting and postprandial antral motility did not differ between patients aged 18–39 and those aged 40–69 years who were being investigated for unexplained gastrointestinal symptoms.[57] Proximal gastric compliance is unchanged in the fasting state in the healthy elderly compared with the young, but perception of gastric distension is diminished,[10] akin to the reduction in visceral sensitivity evident in the oesophagus and stomach. Moreover, proximal gastric accommodation to a meal is delayed compared with young controls, which might contribute to early satiation. Conversely, the antrum is more distended after a nutrient drink in the healthy elderly and antral width correlates with both satiation and satiety in both young and

Table 21.2 Causes of delayed gastric emptying.

Acute
- Drugs (opiates, anticholinergics, L-dopa)
- Postoperative ileus
- Viral gastroenteritis
- Metabolic (hyperglycaemia, hypokalaemia)
- Critical illness

Chronic
- Idiopathic/functional dyspepsia
- Post-surgical (including fundoplication)
- GORD
- Chronic liver disease
- HIV infection
- Endocrine and metabolic (diabetes mellitus, hypothyroidism, chronic renal failure, anorexia nervosa)
- Muscular and connective tissue diseases (myotonic dystrophy, muscular dystrophy, dermatomyositis, systemic sclerosis, amyloidosis, tumour-associated)
- Neurological (central nervous system disease, spinal cord injury, chronic idiopathic intestinal pseudo-obstruction, idiopathic autonomic degeneration)

Table 21.3 Medications with effects on gastrointestinal motility.

Decreased motility or gut transit
- Opiates
- Anticholinergics
- L-Dopa
- Tricyclic antidepressants
- Calcium channel antagonists
- Nitrates
- Phosphodiesterase type 5 inhibitors (e.g. sildenafil)
- Clonidine (an α-2 agonist)
- Sumatriptan (a 5HT-1P agonist)[a]

Increased motility or gut transit
- Metoclopramide
- Domperidone
- Erythromycin (a motilin analogue)[b]
- Beta-blockers
- Selective serotonin reuptake inhibitors

[a]Relaxes the gastric fundus and delays gastric emptying, but increases oesophageal motility.
[b]Stimulates gastric emptying but slows small intestinal transit.

old subjects.[58] EGG recordings are similar in healthy old and young subjects, with subtle differences in the response to nutrients.

There is some evidence for altered responses to the presence of nutrients in the small intestine in the elderly compared with the young. In particular, intraduodenal nutrients stimulate greater cholecystokinin release in the healthy elderly, even allowing for elevated fasting concentrations of CCK in this group,[59] while intraduodenal glucose is more satiating than in the young. This enhanced small intestinal feedback could contribute to both delayed gastric emptying and impaired appetite. Furthermore, there is some evidence that the higher prevalence of *H. pylori* infection and atrophic gastritis in the elderly compared with the young is associated with a decline in levels of the orexogenic peptide ghrelin.[60]

Postprandial hypotension

Blood pressure can decrease markedly after meals in the elderly and this represents an important but often underrecognized clinical problem, leading to syncope and falls.[61] Older people with type 2 diabetes are at particular risk because of the associated autonomic neuropathy. Postprandial hypotension should, in the broadest sense, be regarded as a gastrointestinal disorder, since the postprandial decline in blood pressure appears to be related to the regulation of splanchnic blood flow and the release of gastrointestinal peptide hormones and can be attenuated by administration of the somatostatin analogue octreotide. Among the macronutrients, both carbohydrate and fat contribute to the fall in blood pressure.[62] After oral or small intestinal administration of glucose, the magnitude of the fall in blood pressure is related to the rate at which glucose enters the small intestine.[63] Dietary and pharmacological approaches to slow gastric emptying and small intestinal carbohydrate absorption (e.g. acarbose or dietary interventions such as smaller but more frequent meals) may prove to be effective in the treatment of postprandial hypotension,[64] while distending the stomach (e.g. by drinking a glass of water) can attenuate the postprandial fall in blood pressure.[65]

Small intestine

Although small intestinal function is critical to good nutrition in the elderly, its motility does not appear to be substantially altered with healthy ageing, but can be affected by a number of systemic illnesses.

Changes in small intestinal motor function related to ageing

The small intestine is more difficult to study than the oesophagus or stomach due to its length and relative inaccessibility. Like the stomach, the frequency of its contractions is linked to an underlying electrical rhythm – in this case 8–12 cycles per minute. During fasting, the small bowel undergoes cyclical activity about every 90 min, known as the migrating motor complex (MMC), consisting of motor quiescence (phase I), irregular contractions of increasing frequency (phase II) and a brief period (5–10 min) of regular contractions that propagate distally and serve to sweep

the lumen of debris (phase III). After a meal, the MMC is interrupted by irregular motor activity propagated over short distances that facilitates digestion and absorption.

Small intestinal manometry is carried out in specialized research laboratories and has limited clinical application. Transport through the small intestine can be measured more readily, either by a breath test (which detects an increase in hydrogen resulting from breakdown of ingested non-absorbable carbohydrate, such as lactulose, by colonic bacteria and therefore reflects oro-caecal transit) or by scintigraphy.

MMC periodicity was not altered in healthy elderly volunteers aged 81–91 years compared with the young, using ambulatory jejunal recording, although the propagation velocity of phase III was slower. The elderly had comparable amplitude and frequency of pressure waves to the young during phase III of the MMC and postprandially, but more propagated clustered contractions during fasting and postprandial recordings.[66] The functional significance of the latter phenomenon is unclear, but similar patterns are seen in patients with irritable bowel syndrome. Nevertheless, small intestinal transit in the healthy elderly seems to be comparable to that in the young, in contrast to the delayed transit characteristic of the colon.[8] This is consistent with the observation that small bowel bacterial overgrowth is uncommon in healthy older individuals.[67]

Ageing is associated with an increased prevalence of conditions, such as diabetes mellitus, that potentially affect small intestinal motility, in addition to small intestinal diverticula. Such conditions may induce stasis of small intestinal contents and, together with the reduction in gastric acid secretion often seen on the elderly, predispose to bacterial overgrowth, a potential cause of malnutrition and diarrhoea.[68] However, it should be noted that bacterial overgrowth is rare in the healthy elderly.[69] Small bowel bacterial overgrowth may be diagnosed by culture of duodenal aspirates or by hydrogen breath tests (with glucose or xylose as a substrate), although reports as to their sensitivity and specificity vary widely. A subsequent negative test following a course of antibiotics increases the diagnostic certainty. Treatment is with antibiotics such as metronidazole, tetracycline or quinolones or the non-absorbed antibiotic rifaximin,[70] given for 1–4 weeks and may need to be repeated on a cyclical basis in the event of recurrence. However, there is a paucity of well-controlled data to guide practice in this area.

Systemic disorders associated with disturbance of gastrointestinal motility

Although the effects of healthy ageing *per se* on gastrointestinal motility are modest, the prevalence of co-morbidities increases with advancing age and these may impact on gut function; Parkinson's disease and diabetes mellitus are typical examples. Progressive systemic sclerosis is less common, but has profound effects on gastrointestinal motility. Furthermore, numerous medications can affect gastrointestinal motility; some of these are listed in Table 21.3.

Parkinson's disease

Gastrointestinal dysfunction represents a common manifestation of Parkinson's disease[71] and may both precede and predominate over the somatic motor symptoms.[72] Involvement of the dorsal motor nucleus of the vagus may influence parasympathetic innervation, while abnormalities of the enteric nervous system itself (such as Lewy bodies and loss of dopaminergic neurons) are also evident. Nevertheless, the pathophysiology of gastrointestinal complications of Parkinson's disease has been insufficiently studied and the relative contribution of loss of dopaminergic neurons in the ENS compared with defects of other aspects of neuronal function is unclear.

Dysphagia affects a majority of patients (50–90%), not necessarily in parallel with the duration or severity of other features of the disease. Disturbance of the oropharyngeal phase of swallowing and impaired oesophageal transit, associated with non-peristaltic or tertiary pressure waves, are prominent. Heartburn is a common symptom and could be related to impaired acid clearance. The effects of either L-dopa or anticholinergic therapy on swallowing disorders are inconsistent; both drugs may be associated with either improvement or deterioration of dysphagia. Limited data indicate benefit from apomorphine, which is administered by subcutaneous infusion.

Gastric emptying may be delayed, even in the absence of L-dopa therapy, which in turn slows gastric emptying further. Delayed gastric emptying may contribute to a high prevalence of symptoms such as nausea and bloating and result in impaired nutrition and absorption of oral medications. In particular, L-dopa may be metabolized to dopamine if retained in the stomach and become unavailable for systemic absorption. In patients suffering from the 'on–off' phenomenon of motor fluctuations, gastric emptying may normalize in the 'on' phase, whereas conversely, variations in the rate of emptying may result in erratic L-dopa absorption and in themselves contribute to the 'on–off' phenomenon. Direct infusion of L-dopa into the duodenum has been advocated as a solution to this problem and it has also been suggested that the ratio of dopa decarboxylase inhibitor to L-dopa be increased to improve availability of dopamine both peripherally and centrally.[72] Metoclopramide is contraindicated in parkinsonian patients due to its effects on striatal dopamine receptors, but other prokinetic agents such as domperidone (which does not cross the blood–brain barrier) can be used. Small intestinal, colonic

and ano-rectal dysmotility are also common in Parkinson's disease and may be associated with bowel dilatation and constipation. Oro-caecal transit time is prolonged compared with age-matched controls.

Diabetes mellitus

Diabetes mellitus, particularly type 2 diabetes, is increasing dramatically in prevalence worldwide and occurs frequently in older individuals. Disordered motor function involving all segments of the gastrointestinal tract is common in diabetes and there is a high prevalence of gut symptoms,[73] although there is little information specific to elderly patients with diabetes.[74] Although both disordered motility and gut sensation have been attributed to irreversible autonomic neuropathy, it is now recognized that acute changes in the blood glucose concentration have a major influence on gut function.[75] Studies in a limited number of patients with gastroparesis refractory to medical treatment have revealed losses of both interstitial cells of Cajal, which are responsible for generating the electrical rhythm of the stomach, and myenteric neurons, while staining for inhibitory neurotransmitters is reduced and a few have evidence of gastric myopathy.[76]

In the oesophagus, manometric abnormalities observed in diabetes include a reduction in amplitude of pressure waves, abnormal waves forms and failure of peristalsis, which are associated with delayed oesophageal transit. LOS pressure may be diminished and the prevalence of GORD is increased.

Up to 50% of patients with longstanding diabetes have delayed gastric emptying for solids, liquids or both. Motor correlates of these abnormalities include diminished antral motility and impaired coordination of antroduodenal pressure wave sequences, together with reduced fundic tone. Both the delay in gastric emptying and the underlying motor mechanisms are more marked during acute hyperglycaemia compared with euglycaemia. Disordered gastric emptying potentially contributes to upper gut symptoms, impairs absorption of nutrients and orally administered medications and may result in, and also arise from, poor glycaemic control. Although a delay in gastric emptying may actually improve the postprandial blood glucose profile in non-insulin-requiring patients due to a slower release of carbohydrate to the small intestine, it is likely to result in a mismatch between the absorption of glucose and the onset of insulin action in patients receiving exogenous insulin. Patients with upper gut symptoms referable to the stomach should be investigated with endoscopy to exclude mucosal lesions or obstruction, and consideration can then be given to evaluating the rate of gastric emptying, ideally with scinitigraphy. Diabetic gastroparesis is usually treated with a prokinetic drug, such as metoclopramide, domperidone and erythromycin (an analogue of motilin). The previous agent of choice, cisapride, was withdrawn from many markets due to a risk of cardiac arrhythmia. The role of pyloric injections of botulinum toxin in refractory patients is unclear; a recent retrospective analysis suggested that older patients (aged 50 years or greater) are less likely to benefit than the young,[77] while two trials involving this therapy have not demonstrated any benefit compared with sham injections.[78,79] Similarly, the benefit of implantable gastric electrical stimulators has not yet been adequately demonstrated in controlled trials and, to date, there has been no subgroup analysis of outcomes that specifically addresses efficacy in older patients.

Small intestinal motility is also frequently abnormal in diabetes mellitus. During fasting, the duration of the phases of the migrating motor complex is reduced, whereas postprandially, bursts of non-propagated pressure waves may occur, together with disordered flow patterns of chyme. Small bowel transit appears widely variable in patients with diabetes and its relationship to gastrointestinal symptoms and glycaemic control remains to be clarified. Both diarrhoea and constipation appear common in diabetes; small bowel bacterial overgrowth, coeliac disease and pancreatic exocrine insufficiency should be specifically excluded when patients with diabetes present with diarrhoea. Loperamide and clonidine (an α-adrenergic agonist) may be of benefit when no specific cause of diarrhoea is uncovered, although older patients may be particularly susceptible to adverse reactions (constipation, urinary retention and glaucoma for loperamide; hypotension, bradycardia, sedation and dry mouth for clonidine).

Progressive systemic sclerosis

The peak incidence of progressive systemic sclerosis is in the fifth and sixth decades and gastrointestinal involvement occurs in a majority, affecting multiple regions of the gut, although the correlation between histological involvement and symptoms may be weak.[80] Oesophageal dysmotility has a prevalence of about 80%, with diminished amplitude of pressure waves and sometimes a lack of peristalsis, in the distal (smooth muscle) oesophagus, leading to impaired acid clearance and severe reflux disease. LOS resting pressure also tends to be extremely low. Furthermore, the stomach, small and large intestines and anorectum may be involved, with clinical manifestations of gastroparesis, pseudo-obstruction, bacterial overgrowth (sometimes associated with small intestinal diverticula), malnutrition and constipation or faecal incontinence. Smooth muscle atrophy and fibrosis underlie some of these disturbances,[81] but inhibition of cholinergic transmission in the enteric nervous system by antibodies to M3 muscarinic receptors may be important in the pathogenesis. Similar effects on gastrointestinal motility may be seen in other connective

tissue disorders and in amyloidosis. PPIs are effective in the treatment of GORD, though high-dose therapy may be needed. The role of surgery in refractory reflux symptoms has been controversial, but good results can be achieved.[82] Prokinetic drugs have a role when gastrointestinal transit is delayed.

Functional disorders

Functional gastrointestinal diseases are often potentially overlooked in the elderly.[83] They are characterized by recurrent or persistent symptoms referable to the gut, occurring in the absence of demonstrable organic disease. This group of disorders includes functional dyspepsia (upper abdominal pain, bloating or nausea) and irritable bowel syndrome (IBS) (abdominal discomfort, which may be relieved by defaecation, associated with abnormal bowel habit), and other syndromes related to the oesophagus, anorectum and biliary tract, defined most recently by the Rome III criteria.[84]

The prevalence of IBS appears to be less in the elderly than the middle aged in the United States and United Kingdom[85] and at all ages the prevalence is greater in women than men. Somewhat surprisingly, the incidence, as opposed to prevalence, of IBS appears to increase with age, in at least one US population.[86] This may potentially reflect an increase in healthcare-seeking behaviour in the elderly, although no information regarding consulting behaviour in IBS is available specifically for this age group. In a study of 70-year-olds in a Danish community, although 6–18% had gastrointestinal symptoms consistent with IBS according to various definitions, symptoms had resolved in at least half within the following 5 years,[87] which is probably similar to the prognosis of IBS in the general community. However, it is common for new symptoms to arise in IBS as others resolve.[88] Similar patterns were observed for upper gut symptoms suggestive of functional dyspepsia, indicating that abdominal symptoms are frequent in the elderly, but fluctuate considerably over time. In the general population, around 10% of functional gut disorders follow a bout of infectious gastroenteritis, but recent evidence suggests that the elderly are less prone to developing chronic postinfective symptoms than the young. In contrast to IBS, there is little information regarding the prevalence of functional dyspepsia in older populations.

Although, as discussed, visceral sensitivity seems to decline in healthy ageing, patients with functional dyspepsia or IBS have, as a group, increased sensitivity to gastric and rectal distension. Nevertheless, chronic gastrointestinal symptoms consistent with IBS are common in the elderly, although not markedly greater than in the young, with the possible exception of constipation. Visceral sensitivity has not been studied in the elderly with gut symptoms, nor has tolerance to visceral pain (the lowest level of stimulation at which a subject withdraws or asks to stop). The latter may be relevant, since pain tolerance for somatic stimuli appears to decrease with ageing. The prevalence of *H. pylori* is greater in the older individuals than the young (about 60% at 60 years) but, in the absence of peptic ulceration, its contribution to dyspepsia is controversial.[22]

It is important to exclude organic diseases such as cancer and mesenteric ischaemia when gut symptoms arise in older patients, particularly as the prevalence of organic disease is greater than in the young.[89] For example, when patients present with altered bowel habit, the threshold for colonoscopic investigation should be low. However, it is interesting to note that mesenteric ischaemia seems to occur more often in patients with IBS than those without.[90] Comorbidities such as Parkinson's disease, medications, thyroid disease, diabetes, depression and small bowel bacterial overgrowth must also be considered.

Chronic gastrointestinal symptoms impair quality of life, but many elderly do not present to their doctors, so their impact may go unrecognized in older populations. Depression associated with chronic pain does not appear to be greater in the elderly than the young, but it should be borne in mind that 'gut' symptoms such as anorexia or bowel habit disturbance can also be features of depression. The effects of anxiety on the perception of persistent, as opposed to acute, pain have not been studied closely.[89]

All potential therapies for functional gut disorders must be evaluated against the high placebo response rate (between 20 and 70%) associated with these syndromes, but no clinical trials have focused specifically on the elderly[85] and the potential for adverse effects (e.g. sedation, urinary retention, postural hypotension, blurred vision or glaucoma with tricyclics or hyoscine) needs to be borne in mind in this group. For the management of abdominal pain, the antispasmodics otilonium, hyoscine and peppermint oil[91] and the antidepressants have a good evidence base. The dose of a tricyclic antidepressant used in functional gut disorders is typically lower than standard doses used to treat depression. Selective serotonin reuptake inhibitors may be better tolerated than tricyclics, but there are fewer data regarding their efficacy in IBS and venlafaxine appears less helpful than tricyclics in functional dyspepsia.[92] Probiotics may be of benefit for bloating. Psychotherapy and hypnotherapy have recently shown promise in the management of functional bowel disorders and their efficacy may be comparable to that of pharmacological therapies such as antidepressants,[93] but no information is available about their applicability to the elderly.

When constipation is a feature of IBS, adequate hydration and fibre supplements should be tried, with the caveat that bloating may be exacerbated by a high fibre intake. Osmotic laxatives or lubiprostone (a locally acting type 2 chloride channel activator, which induces intestinal fluid secretion) are other options.[94]

When diarrhoea and faecal urgency predominate, loperamide can be beneficial; a liquid formulation, if available, makes dose titration easier. Alosetron (a 5HT-3 antagonist) may have a place in diarrhoea-predominant IBS in women, but the association of this drug with ischaemic colitis suggests the need to exercise caution, especially in older patients. Randomized controlled trials have included only a few patients over 65 years old. In theory, supplemental fibre should improve the water-holding capacity of stool, but its benefit in diarrhoea has not been proven.

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Key points

- Gastrointestinal motor function is relatively well preserved with healthy ageing, but a general decline in visceral sensation is apparent.
- Systemic illnesses and medication use can often impair gut function in the elderly.
- The consequences of disturbed gut motility and sensation include swallowing disorders, impaired nutrition and absorption of medications and altered bowel habit.
- Functional gastrointestinal disorders are prevalent in the elderly, but organic disease must be rigorously excluded.

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CHAPTER 22

Gastrointestinal bleeding

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Introduction

Gastrointestinal (GI) bleeding is a common, life-threatening condition. The source of GI bleeding could be upper or lower or a combination of both. The type of GI bleeding also varies by amount of bleeding, which could be massive and clinically apparent in the form of haematemesis or haematochezia or it could be hidden or obscure. Upper GI bleeding (UGIB) refers to GI blood loss whose origin is proximal to the ligament of Treitz. Acute UGIB can manifest as haematemesis, coffee ground emesis and the return of bright red blood via nasogastric tube and/or melaena. Haematochezia could occur with UGIB when the bleed is brisk. Lower GI bleeding (LGIB) usually is defined as bleeding distal to the ligament of Treitz.

GI bleeding is a common geriatric problem.[1,2] In the United States, about 350 000 patients are hospitalized for UGIB each year[3] and 35–45% of these are 60 years or older.[4] The incidence of UGIB ranges between 50 and 150 per 100 000 population per year.[5] Women 60 years of age account for 60% of UGIB.[6] The mortality of UGIB has remained at ~6–10% for the last 60 years.[7–9] There is no difference in morbidity and mortality between young and old persons.[10]

The exact incidence of LGIB is not known,[11] but the incidence of hospitalization is about 20–27 episodes per 100 000 persons per year, with a 200-fold increase with advancing age from the second to the eighth decades.[12–14] Most patients with LGIB have favourable outcomes despite advanced age and other comorbid conditions.[15,16]

The mortality for LGIB is 4–10% or greater and is more common with severe bleeding and those undergoing emergency surgery.[17–19] Hospitalized patients admitted for other causes in whom bleeding starts in hospital have significantly higher mortality than those admitted already with LGIB (23 versus 2.4%). The independent predictors of all-cause mortality were increasing age, duration of hospital stay and number of comorbid conditions.[12]

Economic impact

The economic burden of LGIB is not known, but is presumably significantly higher given the prevalence of this disorder in older adults. Thomas *et al*. estimated that diverticular haemorrhage alone cost US$1.3 billion in 2001.[20] The average cost for a patient with LGIB in Canada is approximately US $3000 with an average length of stay of 7.5 days.[21] The estimated direct and indirect cost of peptic ulcer disease exceeds US$9 billion per year.[22]

Clinical presentation

It might be difficult at times to determine the accurate clinical presentation in older people because of poor vision or poor cognition, for example, providing a vague description of haematemesis versus haemoptysis. Haematemesis is defined as vomiting of blood and is caused by UGIB from the oesophagus, stomach or proximal small bowel. The blood may be bright red or it may be old and take the appearance of coffee grounds. Melaena is defined as passage of black, tarry and foul-smelling stools. The black, tarry character of melaena is caused by degradation of blood in the more proximal colon. Haematochezia refers to bright red blood from the rectum that may or may not be mixed with the stool. Occult GI bleeding denotes bleeding that is not apparent to the patient and is caused by small amount of bleeding. However, patients' and physicians' reports of stool colour are often inaccurate and inconsistent.[23] In addition, bright red bleeding, could also be seen be seen from lesions in the right colon.[24]

The manifestation of GI bleeding varies with underlying medical problems; for example, a patient with underlying ischaemic heart disease may present with chest pain after brisk bleeding. Coexisting heart failure, hypertension, renal disease, diabetes, or pulmonary disease may be aggravated by severe GI bleeding, resulting in a shock. Some patients with chronic blood loss may present with signs of

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 22.1 Clinical predictors of poor outcomes risks of rebleeding without endoscopic intervention.

Clinical factors	
Haemodynamic instability (shock, hypotension)	
Bleeding manifested as haematemesis or haematochezia	
Failure of blood to clear with gastric lavage	
Age >60 years	
Coagulopathy	
Presence of underlying serious medical condition	
Hospitalized patients	
Endoscopic factors	*Risk of rebleeding without endoscopic intervention (%)*
Clean base	<3
Flat spot	<8
Adherent clot	30–35
Non-bleeding vessel	Up to 50
Arterial bleeding	Almost 100

anaemia (weakness, pallor, dizziness, fatigue) or cirrhosis and portal hypotension. GI bleeding can also cause hepatic encephalopathy in patients with existing liver disease or develop hepatorenal syndrome. Orthostatic changes may be seen with moderate to severe bleeding.

Clinical course

The hospital course of GI bleeding is similar in both young and older persons. The need for endoscopic therapy, admission to intensive care, blood transfusion requirements, need for surgery and length of hospital stay are not different.[1,10,25] The length of hospital stay shortened from 1970–80 into the 1990s.[25] In 1992 and 1994, the mean hospital stay for UGIB in older adults (>60 years of age) was 6.0 days compared with 5.6 days in those <60 years of age. Table 22.1 describes factors predicative of ulcer rebleeding and clinical factors leading to increased mortality in older adults. The risk of rebleeding is higher for arterial bleeding, adherent clot and non-bleeding vessels compared with clean base and flat spot. Also, mortality rates are higher for arterial bleeding compared with clean base.[26,27]

Causes of GI bleeding

In the elderly, oesophagitis and gastritis in combination with peptic ulcer disease account for 70–91% of hospital admissions for UGIB. A greater percentage of patients with Mallory–Weiss tears, GI varices and gastropathy are seen in the younger population as a result of the greater degree of alcohol abuse in this age group.

Tables 22.2 and 22.3 summarize the site of different studies, number of patients, age and physician by specialty involved for UGIB and LGIB, respectively. Table 22.4 shows the prevalence of UGIB in different studies. The prevalent UGIB causes are gastric ulcer (5–43%), duodenal ulcer (6–42%), gastritis (6–42%), oesophagitis (2–15%), oesophageal varices (1–20%), Mallory–Weiss tear (1–16%) and others (combination of lesions) (2–17%). The common causes of LGIB are summarized in Table 22.5, the prevalent causes being diventricular bleeding (17–56%), angiodysplasia (3–30%), haemorrhoids (3–28%) and polyps (2–30%).

Evaluation and management of GI bleeding

In this section the general evaluation and management of GI bleeding is discussed. For disease specific treatment refer to gastroenterology texts.

Initial evaluation

The first step in the management of GI patients is stabilization with blood transfusion and other treatment deemed necessary before any diagnostic evaluation. If a patient's initial blood pressure and pulse rate are normal, one can consider performing orthostatics to look for volume loss. Orthostatic changes are usually suggestive of 10–20% loss in circulatory volume; although supine hypotension suggests >20% volume loss. Hypotension with a systolic blood pressure of <100 m Hg or baseline tachycardia suggests significant haemodynamic compromise that requires urgent volume resuscitation. All patients require a complete history and physical examination: blood studies (platelet count, prothrombin time, partial thromboplastin time); liver function tests, renal functions and complete blood counts. Determination of blood group and type and cross-match of 2–4 units of blood should be arranged urgently.

Seven independent predictors of the severity of acute LGIB have been identified: hypotension, tachycardia, syncope, non-tender abdominal examination, bleeding within 4 h of presentation, aspirin use and more than two comorbid diseases.[48] These predictors can be helpful in classifying patients into three risk groups. Patients with more than three risk factors had an 84% risk of severe bleeding, those with one to three risk factors had a 43% risk and those with no risk factors had a 9% risk.[32] In a prospective study of patients admitted with LGIB, three predictors of severity and adverse outcome were identified: initial haematocrit <35%, abnormal vital signs and gross blood on rectal examination.[31]

Table 22.2 Studies examining upper gastrointestinal bleeding.

Authors	*N*	Type of study	Physician[a]	Age (years)	Site (hospital)
Palmer (1969)[28]	1400	Prospective	GI	14–94	VA, East Orange, NJ
Crook *et al.* (1972)[29]	768	Retrospective	S	53[b]	Charity Hospital, New Orleans, LA
Allen *et al.* (1973)[30]	71	Prospective?	S/GI	15–84	Henry Ford, Detroit, MI
Sugawa *et al.* (1973)[31]	178	Prospective	S	?	Detroit General Hospital, Detroit, MI
Cotton *et al.* (1973)[32]	208	Prospective	S/GI	2–84	St Thomas, London
Katon and Smith (1973)[33]	100	Prospective	GI	19–84	VA, Portland, OR
Paull *et al.* (1974)[34]	206	Prospective	GI	14–83	Queen Elizabeth, S. Australia.
Katz *et al.* (1975)[35]	200	Prospective	GI	?	Metropolitan Hospital, New York
Lee and Dagradi (1975)[24]	400	Retrospective	GI	29–87	Kaiser Permanente, CA
Katz *et al.* (1976)[23]	1429	Retrospective	GI	?	Metropolitan Hospital, New York
Dagradi *et al.* (1976)[36]	500	Retrospective	GI	40–79	VA, Long Beach, CA
Antler *et al.* (1981)[1]	50	Prospective	GI	55–97	NYMC Metropolitan, New York
Peterson *et al.* (1981)[8]	206	Rand. control	GI	55 ± 0.9[c]	VA + Southern Medical School, Dallas, TX
Silverstein *et al.* (1981)[37]	2097	Prosp. data survey	GI	57 ± 17.5	Private practice
Brolin and Stremple (1982)[38]	624	Retrospective	S	?	Pittsburgh Health Center, Pittsburgh, PA
Bansal *et al.* (1987)[39]	92	Prospective	S/G	65–93	Ryhope General Hospital, Sunderland
Borch *et al.* (1987)[40]	684	?	S	?	Sweden
Tabibian and Sutton (1990)[41]	605	Prospective	GI	?	Ben Taub General Hospital, Houston, TX
Segal and Cello (1997)[10]	200	Retrospective	GI	<60 and older	General Hospital, San Francisco, CA
Vreeburg *et al.* (1997)[42]	1389	Prospective	GI	2–100	Amsterdam
Zimmerman *et al.* (1997)[43]	248	Prospective	GI	64 ± 0.2 84 ± 0.4	Hadassah University Hospital Jerusalem, Israel
Wilcox and Clark (1999)[44]	727	Prospective	GI	50 ± 15.4	Grady Memorial Hospital, Atlanta, GA
Tariq *et al.* (2000)[45]	397	Retrospective	G/GI	60–100	St Louis University Hospital, St Louis, MO

[a]G, geriatrics; GI, gastroenterology; S, surgery.
[b]Mean age.
[c]Values with ± sign = mean with standard deviation.

Table 22.3 Studies examining lower gastrointestinal bleeding.

Authors	*N*	Type of study	Physician[a]	Age (years)	Site (hospital)
Boley *et al.* (1979)[46]	183	Retrospective	GI	≥65	Montefiore Hospital and Medical Center, New York
Caos *et al.* (1986)[19]	35	Prospective?	GI	6–85	University of New Mexico + VAMC, Albuquerque, NM/Portland, OR.
Leitman *et al.* (1989)[17]	68	Prospective?	S	63[b]	New York Hospital–Cornell Medical Center, New York
Jensen and Machicado (1988)[47]	80	Prospective	GI	21–93	UCLA Center for Health Sciences and VAMC, Los Angeles, CA
Makela *et al.* (1993)[18]	266	Prospective	S	24–86	Oulu University Hospital, Oulu, Finland
Richter *et al.* (1995)[15]	107	Retrospective	GI	21–93	Massachusetts General Hospital, Boston, MA
Peura *et al.* (1997)[16]	635	Survey	GI	49–64	Private practice and tertiary teaching hospitals. American College of Gastroenterology Bleeding Registry
Longstreth *et al.* (1997)[12]	2113	Retrospective	Medicine	20–80	Kaiser Permanente Medical Center, San Diego, CA
Wilcox *et al.* (1999)[44]	150	Prospective	GI	?	Grady Memorial Hospital, Atlanta, GA
Tariq *et al.* (2000)[45]	149	Retrospective	GI/G	60–100	St Louis University Hospital, St Louis, MO

[a]See Table 22.1.
[b]Mean age.

Table 22.4 Causes[a] of upper gastrointestinal bleeding (%).

Authors	GU	DU	O	G	D	OV	AVM	MW	GCA	ND	OTH
Palmer (1969)[28]	16	28	7	12	–	19	–	5	–	7	6
Crook *et al.* (1972)[29]	9	42	–	11	–	–	–	1	2	12	5
Allen *et al.* (1973)[30]	27	25	–	25	1	6	1	1	–	10	3
Sugawa *et al.* (1973)[31]	18	11	2	42	1	5	1	15	4	–	–
Cotton *et al.* (1973)[32]	27	21	7	9	1	3	1	1	2	14	–
Katon and Smith (1973)[33]	15	23	13	9	–	16	–	8	15	4	–
Paull *et al.* (1974)[34]	20	32[b]	–	20	5	6	–	6	4	–	17
Katz *et al.* (1975)[c]	5	23	0	22	0	17	–	–	–	22	11
	7	8	4	37	9	7	–	–	–	18	10
Lee and Dagradi (1975)[23]	43[d]	–	–	19	–	–	–	–	–	–	–
Katz *et al.* (1976)[23]	3	21[e]	–	36	–	16	–	–	–	14	13
Dagradi *et al.* (1979)[36]	31[d]	–	–	34	–	16	–	6	2	11	–
Antler *et al.* (1981)[1,f]	29	21	14	17	0	12	–	2	2	–	–
Peterson *et al.* (1981)[8]	18	22	–	6	–	20	–	16	2	12	–
Silverstein *et al.* (1981)[37]	22	23	13	30	9	15	0.5	8	4	–	7
Brolin and Stremple (1982)[38]	10	23	–	34	–	12	–	–	–	15	6
Bansal *et al.* (1987)[39]	25	25	–	22	–	1	–	–	9	3	14
Borch *et al.* (1987)[40]	–	–	–	11	–	–	–	–	–	–	–
Tabibian and Sutton (1990)[41,g]	24	19	15	5	–	25	–	6	0.4	5	2
	22	33	9	3	–	20	1	8	3	1	3
Vreeburg *et al.* (1997)[42]	12	20	7	5	–	9	1	5	3	22	7
Segal *et al.* (1997)[10,h]	35	38	11	7	–	11	–	3	1	–	–
Zimmerman *et al.* (1997)[43,i]	21	36	11	7	–	6	–	–	–	–	–
Wilcox and Clark (1999)[44]	26	24	4	7	–	9	–	6	–	4	10
Tariq *et al.* (2000)[45]	14	6	10	24	13	7	9	3	–	–	16

[a] GU, gastric ulcer; DU, duodenal ulcer; O, oesophagitis; G, gastritis; D, duodenitis; OV, oesophageal varices; AVM, angiodysplasia; MW, Mallory–Weiss tear; GCA, gastric cancer; ND, no abnormality detected; OTH, others.
[b] Pyloroduodenal ulcer.
[c] First row is flexi rigid era and second is panendoscopy era.
[d] Peptic ulcer.
[e] Chronic peptic ulcer.
[f] Only patients aged 55 years and above included.
[g] First row includes patients in county hospital and the second row includes patients in community hospital.
[h] Only patients ≥60 years reported.
[i] Both patient groups added (60–69 and ≥80 years).

Volume restoration

Restoration of intravascular volume is established by inserting two large-bore intravenous peripheral lines with an 18 gauge catheter or central venous line. Fluids used for resuscitation include normal saline, lactated Ringer's solution and 5% hetastarch, with blood transfusion as soon as it is available to improve the oxygen-carrying capacity. Those patients who are in shock may need volume administration using infusion devices or vasopressors if clinically indicated.

Correction of coagulopathy is essential, if possible using fresh frozen plasma to correct/prolong coagulation parameters. Parenteral vitamin K may be used for prolonging prothrombin time from warfarin therapy or nutritional deficiency. Platelet transfusion could be indicated if platelets are low or dysfunctional. Protection of the airways may be needed in circumstances where there is a decrease in mental status (shock, encephalopathy), massive haematemesis or active variceal haemorrhage is present. Antisecretory therapy with a proton pump inhibitor (PPI) is warranted and could be done either orally or intravenously. Antibiotics should also be considered if the patient has underlying cirrhosis.

History

A detailed history could point towards a possible diagnosis. Pain in the epigastric region relieved by food or antacid suggests peptic ulcer disease. Weight loss and anorexia

Table 22.5 Causes[a] of lower gastrointestinal bleeding (%).

Author	D	CCA	AVM	H	IBD	P	C	CU	ND	OTH
Boley *et al.* (1990)[46 b]	34	8	–	7	1	11	3	–	12	17
Boley *et al.* (1979)[46 c]	43	5	20	–	1	4	2	–	11	14
Caos *et al.* (1986)[19]	23	3	20	–	–	14	1	–	23	9
Leitman *et al.* (1989)[17]	26	7	24	2	4	2	6	–	–	9
Jensen and Machicado (1988)[47]	17	11	30	–	–	2	9	–	6	14
Makela *et al.* (1993)[18]	19	10	6	28	8	11	4	–	27	13
Richter *et al.* (1995)[15]	47	10	12	3	3	–	3	–	14	2
Peura *et al.* (1997)[16]	30	8	10	–	8	9	6	–	–	28
Longstreth (1997)[12]	42	9	3	5	2	4	14	–	12	10
Wilcox and Clark (1999)[44]	56	7	5	3	2	2	2	10	4	5
Tariq *et al.* (2000)[45 d]	29	4	6	25	–	30	4	2	–	–

[a]D, diverticulosis; CCA, colon carcinoma; AVM, angiodysplasia; H, haemorrhoids; C, colitis; IBD, inflammatory bowel disease; P, polyp; CU, colonic ulcers; ND, no diagnosis; OTH, others.
[b]Minor bleeding.
[c]Major bleeding.
[d]Percentages of all patients.

may suggest GI malignancy, but in the geriatric population the most common cause of weight loss is depression and should be ruled out before initiating malignancy work-up in non-anaemic and non-bleeding patients. Dysphagia can be due to stricture or cancer of the oesophagus. Mallory–Weiss tears can be caused by intractable vomiting. Haematemesis usually suggests UGIB, but precautions should be taken as older people may have poor vision and be unable to provide an accurate description. Melaena could be seen in both UGIB and LGIB and usually requires about 100 ml of blood. The stool remains positive for blood for almost 2 weeks. Patients with inflammatory bowel disease or infectious colitis (*Shigella, Salmonella, Campylobacter*) usually present with bloody diarrhoea, fever and abdominal pain. One needs to be very cautious in initiating diagnostic work-up in older patients with bleeding diathesis with skin tears and ecchymosis, since this be seen in older patients with minor trauma. Occult blood or haematochezia could be the first sign of colon cancer or polyps. Painless LGIB can also be seen in diverticulosis, angiodysplasia and ulcerated cancerous lesions. Blood on the surface of stool or blood on toilet paper suggests internal haemorrhoids. It is equally important to determine a patient's cognitive ability by using a Mini-Mental Status Examination or Saint Louis University Mental Status Examination to access cognition.[49,50] If a patient is demented then it is advisable to obtain history from the caregiver accompanying the patient or by obtaining history from the nursing home staff.

One should remember to obtain history of aspirin, non-steroidal anti-inflammatory drug (NSAID) and anticoagulation drug use. Some over-the-counter cough medications are usually combined with aspirin and patients may not be aware of it.

Physical examination

A detailed physical examination starting with inspection of the nose and throat is important to exclude bleeding in this area. One should look for signs of chronic liver failure (spider angiomas, hepatosplenomegaly, ascites and jaundice), and also for arteriovenous malformation, especially of the mucous membranes, which may be associated with hereditary haemorrhagic telangiectasia (Rendu–Osler–Weber syndrome), in which multiple angiomas of the GI tract are associated with recurrent bleeding. Cutaneous nail bed and GI telangiectasia may be associated with connective tissue disease or scleroderma. A digital rectal examination is very important to feel for masses and fissures and obtain a sample of stool, to be tested chemically for blood. It is also mandatory to comment on the colour of stools. Internal haemorrhoids, if thrombosed, could be felt by digital examination. If UGIB is suspected, a nasogastric lavage should be performed. Bloody nasogastric lavage is suggestive of UGIB but is negative in about 10% of cases. Coffee ground aspirates indicate bleeding that is slow or has stopped, but bright red blood indicates active bleeding. Continuous nasogastric aspiration help monitor the status of bleeding.

Excluding UGIB

Excluding UGIB is an important step because 2–15% of patients with presumed LGIB will have UGIB. Nasogastric

lavage is a quick and safe procedure but, to avoid unnecessary patient discomfort, it should be reserved for patients with evidence of brisk bleeding in whom an upper endoscopy is not anticipated and risk stratification is needed. Nasogastric lavage containing gross blood, 25% blood-tinged fluid or strongly guaiac-positive dark fluid was found to have 80% sensitivity for bleeding above the ligament of Treitz and positive and negative predictive values of 93% and 99%, respectively.[30] The presence of bile increases the sensitivity of nasogastric lavage,[29] although the correlation between the presence of a bilious aspirate versus presence of bile acids has been questioned.[28] The blood urea nitrogen to creatinine ratio is a non-invasive test also used to help distinguish upper versus colonic sources of bleeding. In one study, a ratio of 33 or higher had a sensitivity of 96% for UGIB, although overlap was observed with LGIB, especially in patients with UGIB without haematemesis.[51] Oesophagogastroduodenoscopy remains the gold standard for excluding an upper GI source in patients presenting with severe bleeding, especially those with haemodynamic instability.

Oesophagogastroduodenoscopy (EGD) can be performed at the bedside in the intensive care unit or in the GI suite and is the preferred method for the investigation and therapy of UGIB. It has the highest diagnostic accuracy and therapeutic capacity and low morbidity. It can be performed early in the clinical course, after the patient is haemodynamically stabilized.

Colonoscopy is performed if the lower GI tract is suspected as a cause of bleeding; its yield is higher if performed in the first 24 h. Colonoscopy is best performed in patients whose condition has clinically stabilized and who can tolerate adequate bowel purge. In order to achieve good results, the patient should be able to drink an adequate bowel prep. Many patients find polyethylene glycol (PEG)-based preparations difficult to take because of the large volume of fluid they are required to consume.

When colonoscopy is negative and LGIB is suspected, *tagged red blood cell (TRBC) scanning* should be considered. RBCs labelled with technetium-99m remain in the circulation for 48 h and extravasate into the lumen with active bleeding. This extravasation is can be detected as a pooling of the radiotracer on scanning with a gamma camera. Bleeding rates as low as $0.1\,ml\,min^{-1}$ can be detected in research settings. When the test is positive, it is accurate in about 80% of cases. About 20% of the localization is false positive, which precludes the use of this test alone for surgical resection of the bowel. The clinical utility of this test is for screening before arteriography.

Arteriography allows localization and potential therapy for GI bleeding when the bleeding rate exceeds $0.5\,ml\,min^{-1}$. It can provide the aetiology, especially bleeding diverticula or angiodysplasia. Angiography can also be used in brisk UGIB when endoscopy is impossible. Embolization of the bleeding artery is infrequently performed because of the risk of bowel infarction. Small-bowel enteroscopes can be used when radiological evaluation suggests a jejunal bleeding source or in recurrent (obscure) GI bleeding in which conventional endoscopy is unrevealing.

Surgery is considered when the blood transfusion requirement exceeds 4–6 units over a 24 h period or 10 units overall, and also with more than two or three recurrent bleeding episodes from the same site. It is prudent to perform colonoscopy before undergoing emergency total colectomy. The extent of comorbid conditions and the degree of bleeding need to be factored in when considering surgery. Therapies for specific lesions are mentioned here that require a different treatment modality than already mentioned.

Variceal haemorrhage

Management of variceal bleeding usually requires intensive care monitoring and endotracheal intubation for airway protection. Octreotide infusion should be initiated immediately ($50–100\,\mu g\,h^{-1}$ bolus followed by an infusion of $25–50\,\mu g\,h^{-1}$). Octreotide is usually well tolerated and reduces portal pressure. Vasopressin is an alternative pharmacological agent but is used less frequently because of the side effects: myocardial ischaemia and infarction, mesenteric ischaemia and infarction, ventricular arrhythmias, cardiac arrest and cutaneous ischaemic necrosis. Concomitant infusion of nitroglycerin is used at times to reduce the undesirable side effects of vasopressin.

Variceal ligation or banding is the endoscopic therapy of choice. It is very effective and superior to sclerotherapy.[52–54] Complications of banding include superficial ulcerations, dysphagia, transient discomfort, transient chest discomfort and rarely oesophageal stricture. *Sclerotherapy* is also effective but is used less frequently because of its complications (ulceration, stricture, perforation, pleural effusion, adult respiratory distress syndrome and sepsis). Recurrent bleeding may be seen in up to 50% of patients but will respond to repeated treatment. Fever may be seen in up to 40% of patients, but if it persist for more than 2 days a bacteraemia test may be necessary.

Transjugular intrahepatic portosystemic shunts (TIPS) have been used in the treatment of complications of portal hypertension. TIPS are used for the control of acute variceal bleeding and prevention of variceal rebleeding when pharmacological therapy and endoscopic therapy have failed. The major limiting factors for TIPS success are shunt dysfunction and hepatic encephalopathy. Because shunt stenosis is the most important cause of recurrent complications of portal hypertension, a surveillance programme to monitor shunt patency is mandatory.[55]

Shunt surgery (portacaval or distal splenorenal shunt) should be considered in patients with good hepatic reserve

if the patient fails endoscopic or pharmacological therapy, having difficulty in returning for follow-up visits, increased risk of death for recurrent bleeding or lives away from medical care. The morbidity and mortality are high with this procedure, as also is postoperative encephalopathy.

Balloon tamponade has a major role in the therapy of variceal haemorrhage. It is used temporarily to stabilize a patient in situations when more definite therapy is available. The commonly used balloon tamponade are the Sengstaken–Blakemore tube and the Minnesota tube, both having a gastric and oesophageal balloon.

Angiodysplasia can occur anywhere in the GI tract and can be occult or overt GI bleeding. Actively bleeding angiodysplasia is best treated by endoscopic therapy (heater probe, laser or organ plasma coagulation), intra-arterial vasopressin or embolization during angiography or surgical resection. Endoscopic ablation is recommended even when non-bleeding angiodysplasia are found in the presence of iron deficiency anaemia. The associated anaemia should be treated with iron.

Stress ulcer is encountered in patients who are in the intensive care unit and on ventilation for more than 48 h with coagulopathy, sepsis, burns and cerebrovascular events. Prophylactic therapy should be administered in patients who are at increased risk. Histamine-2 receptor antagonist, sucralfate and proton pump inhibitors can be used.

Diverticulosis is usually seen on endoscopy, but bleeding develops in about 5% of the patients with diverticula. Bleeding usually stops in these patients 80% of the time but may reoccur. Persistent bleeding may require intra-arterial vasopressin during angiography or even surgical resection.

Aortoenteric fistula is an uncommon but lethal cause of GI bleeding. These patients usually have a history of aortic graft surgery and present with bleeding after surgery. The fistula site is usually aortoduodenal but can be anywhere in the small and large intestine. The classic presentation is herald bleed hours to weeks before massive GI bleeding. Recognition of this condition is essential, as undiagnosed cases could be fatal. Endoscopy with examination of the fourth portion of the duodenum is essential and should be performed immediately. Angiography or computed tomographic scanning may show a leak at the graft site. A negative study does not exclude an aortoenteric fistula. If suspicion is high, a surgical consultation is essential.

Radiation proctitis/colitis results years after exposure to radiation therapy. Intermittent haematochezia results from aberrant superficial mucosal vasculature in the distal colon. Treatment is usually supportive and laser photocoagulation of the mucosal telangiectasias.

Haemorrhoids is the most common cause of haematochezia in outpatient clinics. Treatment is usually avoidance of constipation by using a fibre-rich diet and supportive care. Surgical and endoscopic banding of the haemorrhoids is also available.

Conclusion

GI bleeding is a common geriatric problem. The incidence of GI bleeding is about 35–45% in people 60 years of age and older. The incidence of LGIB is unknown. The causes of GI bleed vary in different studies. The diagnosis and management of GI bleeding are similar to those in young adults in many ways.

Key points

- 40% of persons with GI bleeding are over 60 years of age.
- *Helicobacter pylori* should be excluded in all persons with UGIB.
- Persons with LGIB require endoscopy.
- Angiodyplasia is not uncommon in older persons.

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CHAPTER 23

Liver and gall bladder[1]

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> The liver, that great maroon snail: No wave of emotion sweeps it. Neither music nor mathematics gives it pause in its appointed tasks . . .
>
> (Selzer, 1976)

Age-related hepatobiliary changes

Liver

Traditionally, hepatic biochemical parameters such as serum transaminases, hepatic alkaline phosphatase, γ-glutamyltranspeptidase and serum bilirubin are considered indices of liver function. These parameters, which are indeed more reflective of disrupted hepatocyte integrity and liver dysfunction, are not altered with ageing (James, 1997; MacMahon and James, 1994). However, there is an age-related compromise in more objective and sophisticated dynamic liver function indices. Available data show that with ageing hepatic volume and perfusion may decrease by approximately 30%. Other indices of hepatic metabolic function, such as nitrogen synthesis and aminopyrine clearance, also decrease with ageing. Likewise, age-related reduction in hepatic microsomal cytochrome content may compromise efficient drug metabolism in the elderly (Wynne *et al*., 1989; Fabbri *et al*., 1994; James, 1997).

Histological studies have identified decreased smooth endoplasmic reticulum and fewer mitochondria in hepatocytes from older adults (Schmucker, 1990) Age-related reduction in hepatic regeneration is particularly concerning. Several studies suggest that the older liver is more vulnerable to stress, perhaps due to an age-related reduction in mitogen activated protein kinase activity (Liu *et al*., 1996). These cellular changes contribute to the poorer outcomes observed in older adults following hepatic insult.

Few studies have specifically examined the effect of ageing on the gallbladder and biliary tract. With ageing, there is an increase in the diameter of the common bile duct, due to replacement of biliary ductal myocytes with connective tissue cells (Kialian and Aznaurian, 1995).

In addition, the lithogenicity of bile increases, resulting in an increased tendency to form cholesterol and calcium bilirubinate stones (Siegel and Kasmin, 1997). These preceding changes, set against a background of lifetime exposure to potentially hepatotoxic agents, set the stage for hepatobiliary disease as a major contender in geriatric medicine.

Hepatic diseases of the elderly

Viral hepatitis

Classically, viral hepatitis is defined as hepatic inflammation induced by infection with specific hepatotrophic viruses. Histological features include diffuse or patchy necrosis of the liver acini. Severity of clinical presentation is variable. Some patients are asymptomatic, while others may complain of flu-like and fairly non-specific symptoms such as myalgia, athralgia, anorexia, nausea, vomiting and diarrhoea. Physical examination may reveal fever, jaundice, hepatomegaly and, in some cases, cutaneous manifestations such as purpura, urticaria and other skin lesions.

Geographical distribution and prevalence of viral hepatitis vary with the infecting agent (Figure 23.1).

Hepatitis A virus

Hepatitis A virus (HAV) is a 27 nm single-stranded, non-enveloped RNA picornavirus. Although infection typically occurs by faecal-oral transmission, a few cases of HAV have occurred through haematogenous transmission (Centers for Disease Control and Prevention, 1999). Onset of symptoms is usually 2–6 weeks after exposure. In younger adults, hepatitis A infection is usually subclinical with mild symptoms.

[1]This chapter is as in the Fourth Edition.

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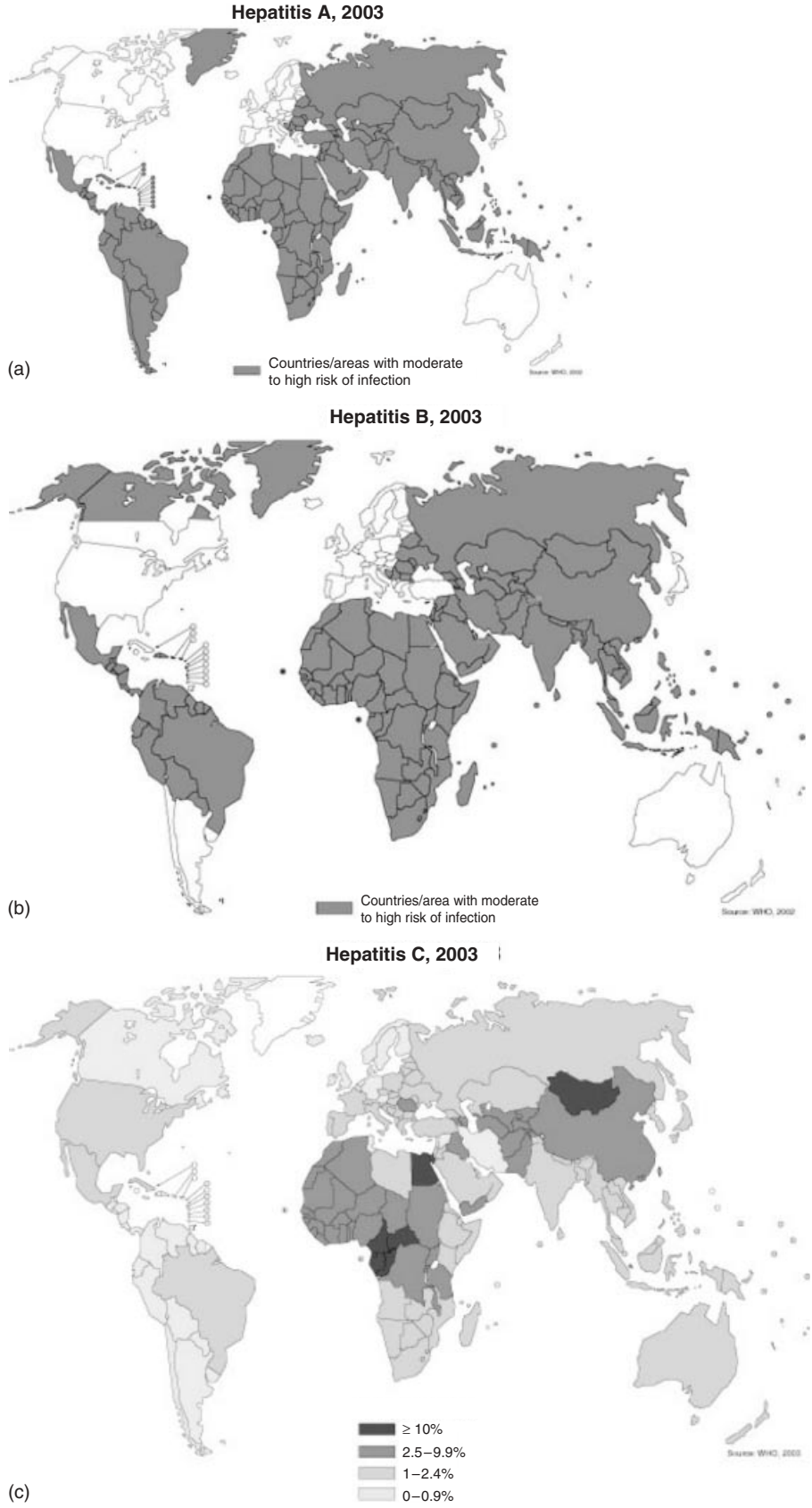


Figure 23.1 Geographical distribution of hepatitis A, B and C.

Jaundice is present in less than 10% of cases. In contrast, although hepatitis A infections are less frequent in older adults, symptoms are likely to be more severe. In addition, the risk of developing and dying from complicating fulminant liver failure is far more common in infected elders. Reported case fatality rate among patients over the age of 65 years is 4% compared with 0.07% in patients aged 15–24 years (Forbes and Williams, 1988). Current recommendations state that older persons travelling to endemic areas should receive HAV vaccination. Additionally elderly food handlers and patients with chronic liver disease are also advised to receive HAV vaccination, although data regarding the efficacy and cost-effectiveness of the vaccine in older adults are lacking (James, 1997).

Hepatitis B virus

Hepatitis B virus (HBV) is a 42 nm double-stranded, enveloped DNA hepadna virus. HBV is a highly infectious virus transmitted through sexual intercourse or contact with infected blood, blood products and saliva. Vertical maternofetal transmission also occurs during childbirth. The incubation period of HBV is approximately 120 days (Lok and McMahon, 2001). Although most infections occur in young adulthood, serological evidence of HBV infection is threefold higher among older adults aged between 64 and 74 years. Rates of HBV infection are also higher among nursing home residents compared to those in community dwelling elders. Sporadic outbreaks of HBV infection in nursing home residents have been linked to inappropriate sharing of razors and bathing appliances. Data indicate that in older adults who contact HBV, the risk of progressing to chronic hepatitis is over 50% compared with 5% following acute infection in younger adults. Nevertheless, acute hepatitis B is rare among older adults, and older adults with acute HBV infection are usually only mildly symptomatic (Marcus and Tur-Kaspa, 1997; Reeder and Halket, 1987). Nevertheless, age remains a risk factor for the development of life-threatening fulminant hepatitis. Perhaps as a result of more prolonged exposure, older adults with HBV infection are more likely to develop hepatocellular carcinoma and liver cirrhosis (Beasley, 1988; MacMahon and James, 1994).

Hepatitis C virus

Hepatitis C virus (HCV) is a 55 nm enveloped RNA flavivirus, with an incubation period ranging from 15 to 90 days. Of the six known genotypes, type 1 is the most common in the United States. Although transmission is primarily haematogenous, a few cases have been transmitted through saliva and human bites (Bukh *et al*., 1995; Chu *et al*., 2002). Data indicate that the prevalence of acute HCV infection among older adults equals, and, in some cases, surpasses that in the general population. Within the United States, reported seroprevalence rate among adults aged over 70 years is 1%, compared with 1.8% among the general population (Alter *et al*., 1999). In an Italian cohort aged over 65 years, the HCV infection prevalence rate was over 4% compared with 3.2% among a comparable cohort of young subjects (Monica *et al*., 1998). Although the incidence of new cases has declined over the past decade, projections indicate that over the next 20–30 years the prevalence of HCV among older adults will increase significantly.

As in younger adults, infection with HCV in elders is only mildly symptomatic during the acute phase. However, the clinical course in older patients is much more aggressive and lethal. Similarly, advanced age at diagnosis of the disease portends more rapid progression to fibrosis and cirrhosis (Seeff, 1997; Watson *et al*., 1996). Other risk factors for the development of cirrhosis include alcohol use and obesity. Studies show that in patients who acquire HCV over the age of 60 years the risk of developing cirrhosis is reported to be as high as 46%, compared to approximately 7% among patients in the fourth decade of life. Reasons for the aggressive clinical course with ageing are not clearly known, although age-related immunocompromise has been proffered as a likely theory (Simmonds *et al*., 1996).

Hepatitis D virus

Hepatitis D virus (HDV) is a single-stranded RNA viroid that is dependent on the HBV envelope protein for replication and pathogenicity. Transmission of HDV occurs haematogenously or through sexual contact and results in either coinfection or superinfection. Coinfection occurs when there is simultaneous transmission of both HDV and HBV, while superinfection refers to HDV infection of a previously HBV positive patient. Patients with coinfections have a better prognosis and progress to chronic disease in less than 5% of cases. In contrast, 70–90% of superinfected patients develop cirrhosis. Although HDV infection causes less than 5% of chronic hepatitis, it accounts for approximately 7500 new infections annually and has a mortality rate of 30% (Alter and Hadler, 1993). Data in older subjects are lacking.

Hepatitis E virus

Hepatitis E virus (HEV) is a single-stranded RNA calicivirus that is transmitted feco-orally. This virus tends to infect younger adults and is rare in developed countries. Characteristically, pregnant women have a 20% mortality rate from this disease compared with 1% in the general population.

Older people travelling to endemic regions such as Asia, Mexico and Africa may be at risk. Prophylaxis is ineffective and the avoidance of consumption of foods and water that may be contaminated is strongly recommended (Gilchrist, 1999).

Hepatitis F virus

Viral particles identified in the stool of post-transfusion, non-A, non-B, non-C, non-E hepatitis cases and injected into Indian rhesus monkeys caused acute hepatitis with elevated transaminases. Consequently, this viral enteric agent was named *hepatitis F virus* (HFV). However, to date there are no convincing corroborating scientific reports. Although sporadic cases in humans may have been identified in Europe, United States, and India, the validity of this virus remains questionable (Deka *et al*., 1994).

GB virus type C (GBV-C)

This virus belongs to the Flaviviridae and was previously referred to as hepatitis G virus (HGV). Currently, the lack of proven association of this virus with either acute or chronic hepatitis has discouraged the use of the name HGV (Dickens and Lemon, 1997). The name GBV-C was derived from a surgeon, whose initials were GB, after marmosets inoculated with his serum developed hepatitis. On the basis of this single observation, the surgeon was erroneously thought to have post-transfusion hepatitis. Later evidence did not support this diagnosis (Almeida *et al*., 1976). Indeed, GB virus type C (GBV-C) infection is common, but is yet to be associated with definite pathogenicity (Dickens and Lemon, 1997). Currently, the major clinical significance of this agent lies in the fact that HIV-positive patients infected with GBV-C may have prolonged survival (Xiang *et al*., 2001). Few data exist regarding the pattern of GBV-C infection in ageing adults.

Transfusion transmitted virus

Transfusion transmitted virus (TTV) is a single-stranded DNA virus. Despite the name, feco-oral transmission of the virus also occurs. Infection is usually acquired in childhood and may persist for years. Its role in causing hepatitis or other diseases has not been proven. Even though one of the genotypes of TTV is suspected to cause hepatitis, the pathogenicity of TTV in humans remains poorly defined (Takacs *et al*., 2003). The prevalence of TTV is also unclear. Available data indicate that the virus has been identified in 1% of blood donors, 18% in post-transfusion subject, 15% of patients with liver cirrhosis and 27% in patients with end-stage liver failure (Naoumov and Petrova, 1998). Notably, high TT virus load has been found to be independently associated with the occurrence of hepatocellular carcinoma among patients with HCV-related chronic liver disease (Nishizawa and Okomoto, 1997).

Autoimmune hepatitis

Autoimmune hepatitis is characterized by severe chronic hepatitis in the presence of circulating autoantibodies. Characteristically, there is frequent progression to liver cirrhosis. Originally described as a disease of young women, autoimmune hepatitis is now known to affect all age groups and both genders. Approximately 20% of all patients diagnosed with autoimmune hepatitis are over the age of 65 years (Newton *et al*., 1997). Diagnostic criteria for autoimmune hepatitis are unchanged with age, and the prognosis for affected older adults is no worse than for younger adults (Table 23.1). Nonetheless, older adults present with less acute symptoms, but are more likely to have severe histological inflammation and necrosis. Unfortunately, data indicate that older adults are less likely to be prescribed immunosuppressive therapy, even though this has been shown to prolong survival in patients with severe disease. There are no data to support the benefits of therapy in older adults with mild disease (Czaja and Freese, 2002).

Drug-induced hepatitis

Several unique factors predispose the elderly to drug-induced hepatotoxicity. These include polypharmacy and, subsequently, an increased risk of drug-induced adverse effects and drug–drug interactions. Age-related physiological changes, such as reduced liver mass, hepatic hypoperfusion and reduced activity of phase 1 hepatic drug-metabolizing enzymes, further increase the likelihood of hepatic injury in response to toxic drugs. Age-related changes in body composition may compromise the volume of distribution, thereby increasing serum drug levels. Hypoalbuminaemia resulting from excess cytokine elaboration, related to ageing or disease, may reduce protein binding and further increase the likelihood of drugs attaining toxic levels. Finally, altered pharmacodynamics with ageing affect the response to drugs at the tissue level (Regev and Schiff, 2001; Varanasi *et al*., 1999).

Not surprisingly, drug-induced liver disease occurs more frequently, and is more severe, in older adults. In addition, older patients with coexisting renal or hepatic disease are more likely to be affected. Documented prevalence of drug-induced hepatitis ranges from 50 to 140 per 1 million person-years in adults aged between 70 and 79 years (Almdal and Sorensen, 1990; Sgro *et al*., 2003). Overall, the incidence of drug-induced liver disease may be higher in older adults simply because these drugs are used more frequently. Non-steroidal anti-inflammatory drugs (NSAIDs) are used extensively by older adults for a variety of arthritic and non-arthritic conditions. All NSAIDs are potentially hepatotoxic. Nevertheless, the reported rate of NSAID-induced hepatotoxicity is less than 1%. Affected patients are usually asymptomatic, with elevated hepatic transaminases. Hepatic alkaline phosphatase may also be mildly elevated. Notably, patients with piroxicam-induced hepatitis may present with severe cholestatic features. NSAID hepatitis

Table 23.1 Diagnostic criteria for autoimmune hepatitis (Alvarez *et al*., 1999; Czaja and Freese, 2002).

Criterion	Definite	Probable
Genetic liver disease	Normal α1-antitrypsin, ceruloplasmin, iron and ferritin levels	Partial α1-antitrypsin deficiency, non-specific serum copper, ceruloplasmin, iron and ferritin abnormalities
Viral infection	No markers of current infection with HAV, HBV, HCV	No markers of current infection with HAV, HBV, HCV
Toxic or alcohol injury	Daily alcohol $<25\,g\,day^{-1}$ and no recent use of hepatotoxic drugs	Daily alcohol $<50\,g\,day^{-1}$ and no recent use of hepatotoxic drugs
Laboratory features	Predominant serum aminotransferase abnormality, globulin, gamma-globulin or immunoglobulin G level >1.5 times normal	Predominant serum aminotransferase abnormality; hypergammaglobulinaemia of any degree
Autoantibodies	ANA, SMA or anti-LKM1 >1:80; no AMA	ANA, SMA or anti-LKM1 >1:40, or other autoantibodies[a]
Histological findings	Interface hepatitis No biliary lesions, granulomas or prominent changes suggestive of another disease	Interface hepatitis No biliary lesions, granulomas or prominent changes suggestive of another disease

[a]Perinuclear antineutrophil cytoplasmic antibodies, antibodies to soluble liver antigen/liver pancreas, actin, liver cytosol type 1 and asialoglycoprotein receptor.
ANA, antinuclear antibody; SMA, smooth muscle antibody; LKM, liver kidney microsomal antibody; AMA, antimitochondrial antibody.

usually responds well to withdrawal of the offending agent. All older adults started on NSAIDs should have their liver function evaluated within two to three months of starting therapy (Hepps *et al*., 1991; Solomon *et al*., 2003).

Following a decline in the use of methyldopa, hepatic disease associated with the use of cardiac medications exhibited a decline. However, with the increased use of amiodarone, hepatocellular disease related to cardiac medications has begun to increase. Affected patients are usually asymptomatic. Approximately half of all patients on amiodarone exhibit a rise in serum transaminase levels. Amiodarone-induced hepatitis may occur with both oral and intravenous administration. These changes resolve if amiodarone is withdrawn early in the course of treatment. Other histological findings of amiodarone-induced hepatitis include steatohepatosis, cholestatic hepatitis and micronodular cirrhosis (Tameda *et al*., 1996; Traverse *et al*., 1994; Gonzalez Galilea *et al*., 2002)

With most medications, the increased prevalence of drug-induced hepatotoxicity in older adults is a consequence of increased exposure. However, certain drugs such as benoxaprofen, halothane and several antituberculous agents – isoniazid (INH), rifampicin and pyrazinamide – are inherently more likely to cause hepatotoxicity in older adults (Varanasi *et al*., 1999; Nagayama *et al*., 2003). Benoxaprofen is a non-steroidal agent, which was withdrawn by the United States Food and Drug Administration (FDA) following several reports of fatal liver failure occurring specifically in adults over the age of 70 years. Similarly, animal studies indicate an age-related increase in sensitivity to the effects of halothane, resulting in an increased risk of hepatic failure and death among older adults exposed to this agent.

INH hepatitis is rare in young patients but occurs in more than 2% of patients aged over 50 years. Increased sensitivity to INH in older adults is related to changes in hepatic physiology and altered pharmacokinetics. INH metabolism produces toxic reactive metabolites presumably from acetylation. Traditionally, persons with the rapid INH acetylator phenotype were considered more prone to toxicity. Most recent studies have failed to confirm this relationship. Indeed, convincing data suggest that slow acetylators may divert larger amounts of INH to an alternative metabolic pathway (cytochrome P450 2E1) that results in production of a toxic reactive metabolite (Huang *et al*., 2003). The precise mechanism underlying INH toxicity is still unknown.

Presenting features of INH toxicity range from asymptomatic elevation of transaminases to fulminant hepatic failure requiring liver transplantation (Vasudeva and Woods, 1997). Thus, patients on INH should receive serial serum transaminase measurements to facilitate early detection of hepatotoxicity.

Diagnosis and management of hepatitis

Clinical presentation of hepatitis varies widely and affected patients may be entirely asymptomatic. Some patients present with flu-like symptoms, such as fever, chills, skin rash, nausea, vomiting, myalgia, arthralgia or malaise. System-specific symptoms such as jaundice, abdominal discomfort, dark urine, easy bruising, and hepatomegaly may also occur. Certain hepatitides, such as hepatitis C, are

characteristically asymptomatic during the acute phase. Diagnosis in such cases is usually delayed until several years after infection. In autoimmune hepatitis, despite the chronic nature of the disease, 40% of patients present acutely with fever, jaundice, polyarthralgias, myalgias, thrombocytopenia and biochemical evidence of severe hepatic dysfunction (Krawitt, 1996).

Serum testing in most cases of hepatitis will reveal elevated transaminases. In mild cases, elevation usually does not exceed three times normal, while in severe cases there may be a 20-fold increase. Clinical detectable jaundice is usually not present until serum bilirubin exceeds 3 mg dl^{-1}. With severe disease, prothrombin time increases, and this is usually indicative of impending liver failure. Additional blood testing should be done in all cases to determine the a etiology of the hepatitis. Thus, viral antigen and antibody studies are conducted to screen for hepatitis A–E. GBV-C RNA may be identified using a reverse transcriptase polymerase chain reaction test. This test is not available for commercial use. There are also no serological assays routinely available for the diagnosis of GBV-C (HGV) or TTV (Stapleton, 2003).

An autoantibody profile for circulating autoantibodies should be conducted to screen for autoimmune hepatitis. Most patients will have elevated levels of circulating autoantibodies. However, only two-thirds will have one of the more specific autoantibodies. Patients are frequently screened for antinuclear and/or antismooth muscle antibodies (Lohse *et al*., 1995; Czaja and Freese, 2002). Tests for other autoantibodies such as soluble liver antigen, liver cytosol antigen and the asialoglycoprotein receptor antibody are also helpful diagnostic tools with high specificity (Manns *et al*., 1987; Martini *et al*., 1988; Treichel *et al*., 1994). Laboratory tests for autoimmune hepatitis should include serum protein electrophoresis. This may reveal hypergammaglobulinaemia with a selective increase in IgG levels. Human leukocyte antigen (HLA) typing may be helpful as most patients are positive for HLA B8, DR3 or DR4 (Donaldson *et al*., 1994).

The diagnosis of drug-induced hepatitis is usually one of exclusion based on the patient's medication history, which should include questions pertaining to the use of prescription, over-the-counter and herbal medications.

Imaging techniques, such as ultrasound, computed tomography (CT) scans, and MRI are helpful in further evaluation of patients with suspected hepatitis for a etiology and severity of disease. Definitive diagnosis, assessment of severity, acuity and activity of disease are based on histological findings and require a liver biopsy.

On the basis of liver biopsy findings, hepatitis may be characterized as acute or chronic. Autoimmune hepatitis and all the viral hepatitides except HAV, HEV and HFV exist in both the acute and chronic phases. Histologically, chronic hepatitis may be further characterized into four stages: (i) chronic persistent to mild chronic active hepatitis; (ii and iii) chronic active hepatitis with scarring; and (iv) cirrhosis (Bach *et al*., 2000). Rapidity of clinical progression through these stages cannot be predicted.

The cornerstone of treatment of any hepatitides is primarily supportive care. Rest, adequate nutrition and avoidance of additional injury from alcohol or other toxic insults should be stressed. Currently no specific medication is recommended for hepatitis A, D, E or G. In 25–50% of patients with chronic HBV infection, treatment with interferon α-β results in disease remission within 6 months. Oral nucleoside analogues, such as lamivudine and famciclovir, have been shown to reduce HBV levels and the risk of fulminant hepatic failure in more than 50% of patients treated with these agents (Hoofnagle and DiBalart, 1997; Lai *et al*., 1998). The decision to treat patients with HCV is usually made on an individual basis, using factors such as compliance, disease severity, and likelihood of favourable response. Standard therapy consists of pegylated interferon alpha and ribavarin. Following 24 weeks of therapy, undetectable levels of HCV RNA are achieved in over 50% of patients, indicating a sustained response. Patients infected with HCV genotype 1 are less likely to respond, with only 42–46% of patients achieving a sustained response with treatment. Forty-eight weeks of therapy is advised to maximize chances of favourable response. Patients infected with HCV genotype 2 or 3 have a sustained response exceeding 75% and generally require only 24 weeks of therapy. If HCV RNA remains detectable following the course of treatment, therapy should be discontinued, as less than 2% of patients will subsequently respond (Manns *et al*., 2001; Fried *et al*., 2002; Hadziyannis *et al*., 2002).

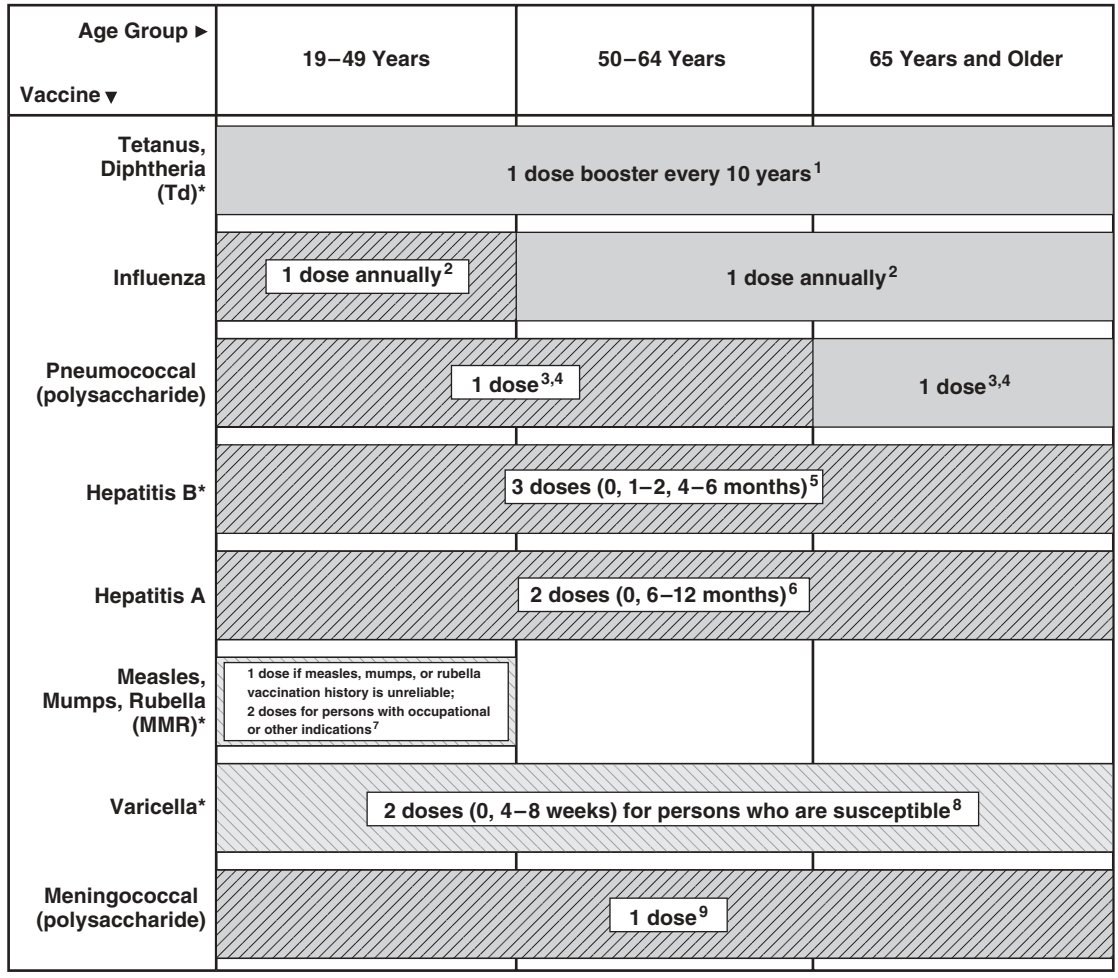
Currently vaccinations are available only for HAV and HBV (Figure 23.2).

Patients with severe autoimmune hepatitis [aspartate transaminase (AST) > 10-fold or AST>fivefold and serum gamma globulin>twofold] are definite candidates for treatment. Combination therapy using azathioprine and corticosteroids has been shown to prolong survival and improve outcomes in affected adults. Patients with mild autoimmune hepatitis do not benefit from treatment (Newton *et al*., 1997).

Alcoholic liver disease

Excessive alcohol use is a major cause of liver disease. Approximately 10% of men and 2% of women over the age of 60 years suffer from an alcohol use disorder. Although age does not alter alcohol dehydrogenase activity, studies suggest a difference in the clinical course and outcomes of alcoholic disease in older adults compared with younger subjects. Older adults who present with alcoholic liver disease are more likely to have severe symptoms and present with complications such as portal hypertension or liver

Recommended Adult Immunization Schedule, United States, 2003–2004 by Age Group



See Footnotes for Recommended Adult Immunization Schedule, by Age Group and Medical Conditions, United States, 2003–2004 on back cover

For all persons in this group | **Catch-up on childhood vaccinations** | **For persons with medical/ exposure indications**

*Covered by the Vaccine Injury Compensation Program. For information on how to file a claim call 800-338-2382. Please also visit www.hrsa.gov/osp/vicp To file a claim for vaccine injury contact: U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington D.C. 20005, 202-219-9657.

This schedule indicates the recommended age groups for routine administration of currently licensed vaccines for persons 19 years of age and older. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

Report all clinically significant post-vaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available by calling 800-822-7967 or from the VAERS website at www.vaers.org.

For additional information about the vaccines listed above and contraindications for immunization, visit the National Immunization Program Website at www.cdc.gov/nip/ or call the National Immunization Hotline at 800-232-2522 (English) or 800-232-0233 (Spanish).

Approved by the Advisory Committee on Immunization Practices (ACIP), and accepted by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Physicians (AAFP)

Figure 23.2 Summary of recommendations published by The Advisory Committee on Immunization Practices – Centers for Disease Control, Department of Health and Human Services.

cirrhosis. Prognosis in older patients is directly related to age. Patients presenting with alcoholic liver disease over the age of 70 years have a mortality rate at one year of about 75% compared with 5% in patients aged less than 60 years (Varanasi *et al*., 1999; Beresford and Lucey, 1995; Corrao *et al*., 1997; James, 1997)

Laboratory testing reveals elevated serum aspartate aminotransferase, bilirubin and alkaline phosphatase. Liver biopsy reveals a spectrum of histological changes ranging from steatosis, through acute hepatitis to cirrhosis. Animal models indicate that toxic oxidative stress and proinflammatory cytokine elaboration, arising from metabolism of ethanol to acetate, contribute significantly to the onset of alcohol-related steatosis and progressive forms of liver damage. Elevated serum concentration levels of tumour necrosis factor alpha (TNF), interleukin (IL)-6, IL-8, IL-18 and transforming growth factors occur in patients with alcoholic liver disease. Cytokine levels have been shown to correlate with liver dysfunction and clinical outcome. Cessation of alcohol intake results in resolution of steatosis and restoration of normal hepatic architecture within a few weeks. Acute alcoholic hepatitis, which comprises cellular inflammation and fibrosis, also responds to alcohol cessation. Persistent alcohol intake results in progressive fibrosis and subsequent cirrhosis within 5 years in 40% of affected patients (McClain *et al*., 2004; McClain *et al*., 1999).

Treatment of alcoholic liver disease does not vary with age. Abstinence is the cornerstone of effective management and is critical to the success of all other adjunctive therapy. Most patients with alcohol dependence are undernourished, which further increases their mortality risk. Severely undernourished veterans with acute alcoholic hepatitis had a 30-day mortality rate of 52% compared with a 2% mortality rate in their counterparts with only mild undernutrition. Protein energy undernutrition compromises the immune system and may therefore have a permissive effect on the toxicity of alcohol. In addition, hepatic regeneration may be compromised by impaired protein synthesis. Thus, aggressive nutritional support is recommended for patients with alcoholic liver disease.

Corticosteroids have been shown to ameliorate cytokine production, suppress acetaldehyde catabolism and thereby blunt the hepatic inflammatory response. Nevertheless, data from several meta-analyses have failed to demonstrate consistent benefit from corticosteroid therapy in alcohol-related liver disease. Paucity of data in addition to potential side effects of steroid therapy in older adults renders steroid therapy an unwise choice in older adults. Several research studies are aggressively exploring the role of cytokine antagonism in the treatment of alcohol liver disease. Theoretically, TNFα antagonists could prove useful in suppressing alcohol-related hepatic inflammation. Recent studies suggest that anti-TNF therapy may improve histological features and enhance survival (Spahr *et al*., 2002; Tilg *et al*., 2003). However, well-controlled randomized trials are lacking. Pentoxifylline, a phosphodiesterase inhibitor, has proved useful in reducing the risk of hepatorenal syndrome (Akriviadis *et al*., 2000).

Several studies have evaluated the effect of antioxidants, such as *S*-adenosylmethionine and silymarin (milk thistle), in the treatment of alcoholic liver disease. Available evidence fails to confirm benefit from any of these agents (Pares *et al*., 1998; Mato *et al*., 1999). Other potentially antioxidative agents such as propylthiouracil and phosphatidylcholine have also been studied. They had no effect on outcomes or survival (Rambaldi and Gluud, 2001; Lieber *et al*., 2003). Colchicine, an inhibitor of collagen synthesis, produced a paradoxical increase in the risk of adverse events (Rambaldi and Gluud, 2001).

Hepatocellular carcinoma

In North America, hepatocellular carcinoma is predominantly a disease of older adults, with 50% of cases occurring in adults over the age of 60 years. In contrast, the peak incidence of hepatocellular carcinoma (HCC) in Sub-Saharan Africa and China occurs in young to middle adulthood. Older adults are more likely to present with advanced disease and their survival rates are significantly lower than those of younger patients (10.5 weeks compared with 18.5 weeks in younger adults Collier *et al*., 1994; Regev and Schiff, 2001).

Hepatocellular carcinoma in older adults is more likely to be related to HCV than HBV (Hoshida *et al*., 1999). Data from a Korean study identified a serological positivity ratio of 29.7 for hepatitis B surface antigen in patients younger than 50 years compared with 0.9 in patients older than 60 years (Lee *et al*., 1993). Infection with HBV in the earlier years of life as opposed to in adulthood, as is the case with HCV, probably accounts for this difference. Additionally, the latent interval between acquisition of HCV and the development of hepatocellular carcinoma is significantly longer than with HBV.

Available data indicate that treatment outcomes of hepatocellular carcinoma are unaffected by age. There is difference in morbidity, early mortality or long-term survival between older and younger patients treated with either surgical resection or chemo-embolization (Bismuth, 1999; Hanazaki *et al*., 2000). Thus, age should not be used as the sole determining criterion for deciding treatment options.

Diseases of the gallbladder and biliary tract

Gallstone disease

Age-related changes in biliary metabolism result in increased cholesterol saturation of bile and gallbladder

dysmotility. In addition, there is increased activity of HMG-CoA reductase and reduced activity of 7-*alpha*-hydroxylase. These changes enhance the lithogenicity of bile. Consequently, there is an increase in the prevalence and severity of gallstone disease, specifically cholesterol, and calcium bilirubinate stones, in older adults (Bowen *et al*., 1992; Affronti, 1999).

In the United States, the incidence of gallstones in Caucasian women increases from 5% in the third decade of life to 25% in the seventh decade. Complications such as choledocholithiasis, emphysematous cholecystitis, ascending cholangitis and pancreatitis are more apt to occur with ageing. Although the precise reasons are yet to be defined, it has been proffered that atherosclerosis in older adults may cause gallbladder ischaemia, thereby enhancing susceptibility to disease (Kahng and Roselyn, 1994).

Clinical features

Although asymptomatic cholelithiasis is a common occurrence in older patients, most of them never experience complications. However, in older adults the frequent coexistence of multiple illnesses and the atypical presentation of diseases render complications more sinister and possibly life threatening when they do occur. Approximately one-fifth of older adults presenting with cholecystitis are likely to have coexisting choledocholithiasis and biliary colic, compared with about 5% of younger subjects. Ascending cholangitis is also more likely to occur in older patients. Following emergent cholecystectomy, approximately 50% of older subjects will develop choledocholithiasis (Siegel and Kasmin, 1997; Reiss and Deutsch, 1985; Rosenthal and Anderson, 1993).

Older adults are more likely to manifest with atypical features that may confound early diagnosis. Blunted febrile responses and minimal leukocytosis in the face of infection may delay diagnosis of cholecystitis. Abdominal pain in patients with impaired cognitive function may be poorly localized. Data indicate that in patients over the age of 65 years, 56% may be afebrile on presentation, 84% have poorly localized abdominal pain and 5% may be completely pain free. Delirium resulting from infection in cholecystitis may misdirect clinical focus toward the nervous system.

Physical diagnosis is less accurate in older patients. Murphy's sign in older adults is poorly sensitive (48%) compared with a sensitivity of 90% in younger patients. In older patients, Charcot's triad (right upper quadrant pain, jaundice and fever) is more likely to present as Reynold's pentad with the additional features of delirium and hypotension (Hendrickson and Naparst, 2003; Parker, 1997; Adedeji, 1996). The onus rests with health professionals to maintain a keen sense of awareness of the likelihood of this disorder in older patients.

Diagnosis and management

Ultrasound is the imaging modality of choice in suspected cholelithiasis and cholecystitis. However, health professionals should be aware that older adults have a higher incidence of acalculous cholecystitis, which may not be identified on ultrasound. Utilization of hydroxy iminodiacetic acid (HIDA) scans as an adjunct in such cases may be helpful. Increasingly sophisticated endoscopic procedures have considerably enhanced diagnostic and therapeutic options in biliary tract disease (Hendrickson and Naparst, 2003). Ideally, an endoscopic retrograde cholangiopancreatography (ERCP) should always precede a cholecystectomy to facilitate accurate definition of the required surgical procedure. Endoscopic ultrasound is a newer technique that is just as sensitive as, but less risky than, ERCP. This may become the preferred procedure for older frail patients (Canto *et al*., 1998).

ERCP is a safe and effective procedure in older adults. With experienced operators, the success rate is approximately 98%. Evidence suggests that older adults tolerate ERCP better than younger patients. In a cohort of 64 patients over the age of 90 years undergoing therapeutic ERCP, Kasmin *et al*. 1995 identified a complication rate of 3% with no incidents of pancreatitis and no procedure-related deaths. Within the general population the expected overall complication rate ranges from 5 to 10% (Affronti, 1999).

Newer techniques such as endoscopic ultrasound, intraductal ultrasonography, magnetic resonance cholangiopancreatography and three-dimensional computed tomography continue to improve diagnostic accuracy (Domagk *et al*., 2004).

Adoption of a 'wait and see' approach is advocated as a reasonable therapeutic option in the management of cholelithiasis. However, data to support this were derived from studies of younger patients. The increased risk of complications and mortality following emergent surgery make this a less favourable solution for older adults. Reported mortality rates for elective procedures range from 4 to 10%, which are comparable to data obtained from younger adults. In emergent situations the mortality rate in older patients rises as high as 20% (Rosenthal and Anderson, 1993). Accordingly, the risks of expectant therapy in older adults with apparently asymptomatic disease must be carefully weighed against the benefits of elective intervention.

Laparoscopic cholecystectomy is the preferred therapeutic option in symptomatic cholelithiasis. Advantages of this procedure over open cholecystectomy include reduced length of stay and less patient discomfort. Anecdotal reports suggests that this minimally invasive procedure is well tolerated by older adults who are otherwise reasonable candidates for surgery. However, studies have yielded

conflicting results with regard to morbidity and mortality data. The decision to perform laparoscopic cholecystectomy is still operator dependent. Nevertheless, increased proficiency at this procedure is rapidly relegating open cholecystectomy to the position of a salvage procedure following failure of a laparoscopic cholecystectomy (Kahng and Roselyn 1994; Ido *et al*., 1995).

Pharmacological dissolution has rapidly fallen out of favour as a viable primary therapeutic option. Chenodeoxycholic acid was the first agent developed to reduce lithogenicity of bile and dissolve gallstones. Complete dissolution was rarely achieved and occurred in less than 15% of patients. Added disadvantages to the use of this agent were a high recurrence rate (50%), significant adverse effects and high cost. A newer and similar agent, ursodeoxycholic acid, is better tolerated and may be more effective. However, definitive evidence in older adults is lacking (Kahng and Roselyn 1994; Weinstein *et al*., 1990).

Similarly, there is a striking lack of data concerning the safety and efficacy of contact dissolution in older adults. Methyl *tert*-butyl ether (MTBE), a potent cholesterol solvent, is instilled into the gallbladder during percutaneous transhepatic cholangiography to facilitate direct contact dissolution of gallstones. Catheter-related complications, MTBE toxicity, the high recurrence rate and the virtual absence of any data in older adults render this an inadvisable and obsolete option (Thistle and May, 1989).

Finally, biliary electroshock wave lithotripsy is a non-invasive procedure that appeared to be a potentially favourable option for older adults. However, the efficacy of this technique depends on multiple factors, including size, calcium content and number of stones, and adequate gallbladder function and motility. Few patients qualify for this procedure (Magnuson *et al*., 1989). There are no data in elders.

Gallbladder perforation

Gallbladder perforations are more likely to occur in the fundus because, compared with the rest of the gallbladder, the fundal portion is relatively poorly vascularized. Type 1 gallbladder perforations are acute and associated with biliary peritonitis. Type II perforations are subacute and characterized by the presence of a pericholecystic abscess. Type III perforations generally result in a fistulous tract between the gallbladder and the duodenum.

Type III perforations occur most frequently and are more likely to be complicated by gallstone ileus. Although uncommon in the general population, gallstone ileus is the commonest cause of small bowel obstruction in older women, occurring in 25% of such cases. Definitive management is surgical enterotomy and stone extraction (Kahng and Roselyn, 1994)

Emphysematous cholecystitis

This is a life-threatening condition characterized by gangrene of the gallbladder due to an infection with gas-forming organisms. Emphysematous cholecystitis is more likely in older patients with diabetes. Clostridial organisms are implicated in most patients. Cholelithiasis is present in only half of affected patients. Ischaemia has been implicated in this condition although the precise pathogenetic mechanisms remain unclear. Mortality is very high and emergent cholecystectomy is indicated (Affronti, 1999).

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune disease characterized by progressive destruction of intrahepatic biliary ducts and chronic cholestasis. Although predominantly a disease of middle-aged women, over one-third of patients are over the age of 65 years (Metcalf *et al*., 1997). Several large case series indicate that the mean age at presentation is approximately 60 years with the peak incidence occurring between 70 and 79 years (Metcalf *et al*., 1997; Howel *et al*., 1997).

In patients who are symptomatic at presentation, advanced age is an independent adverse prognostic factors (Regev and Schiff, 2001). Treatment is generally reserved for selected older patients who are symptomatic. Outcomes for asymptomatic patients do not differ from that of the general population. Asymptomatic patients often come to attention following investigation of an unexplained elevation of serum alkaline phosphatase. Diagnosis of PBC is usually confirmed by the detection of antimitochondrial antibodies. Extrahepatic manifestations of PBC include hypothyroidism, sicca syndrome, hypothyroidism and cutaneous xanthoma. Fat-soluble micronutrient deficiencies may occur, resulting in an increased risk of osteoporosis and impaired coagulation (James, 1997).

Medical therapy is not very helpful in treating PBC. Colchicine may retard progression of liver fibrosis and improves laboratory values in patients with PBC but it has no effect on signs or symptoms of the disease. Corticosteroids and D-penicillamine are ineffective treatment options. Conflicting results have been obtained regarding other immunosuppressive agents such as azathioprine (Imuran), methotrexate and ciclosporin A. Ursodeoxycholic acid is a promising pharmacological agent. Data demonstrate not only improved symptoms and biochemical parameters but also retarded progression of PBC following ursodeoxycholic acid therapy. Recent evidence also suggests a role for selective estrogen receptor modulators in the treatment of PBC. Tamoxifen therapy has been associated with a decrease in serum alkaline phosphatase level in two women with coexisting PBC. Authors of these case reports suggest that tamoxifen may act on cholangiocyte

estrogen receptors to inhibit cholangiocyte proliferation. Further evidence is needed to support this hypothesis (Bergasa *et al*., 2004; Reddy *et al*., 2004). In contrast, orthotopic liver transplantation has very good outcomes in patients with end-stage liver disease resulting from PBC (Bergasa *et al*., 2004).

Liver transplantation

Liver cirrhosis, portal hypertension and liver failure have a major impact on both hepatic and all-cause mortality in older adults. Indeed, the presence of liver cirrhosis in the setting of concomitant disease is an adverse prognostic factor. Subjects with chronic liver disease and complicating cirrhosis aged over 80 years had a cumulative survival rate of 59 and 19% at 5 and 9 years, respectively, compared with 86 and 69% in their non-cirrhotic counterparts with chronic liver disease (Hoshida *et al*., 1999; del Olmo *et al*., 2000; O'Mahony and Schmucker, 1994). Although management of liver cirrhosis in older adults is similar to that in younger adults, long-term survival rates are much worse in the elderly.

Previously, advanced age was considered a contraindication to liver transplantation and patients older than 55 years were rarely accepted as transplant recipients. More recent evidence indicates a survival rate among older transplant recipients comparable to that of younger subjects. Age, as an isolated criterion, is therefore no longer considered a contraindication to liver transplantation (Tran *et al*., 2004; Fattovich *et al*., 1997).

Currently, approximately 20% of transplant recipients in the United States are over the age of 60 years compared with less than 10% in 1989 (Seaberg *et al*., 1998). Additionally, quality of life, morbidity and one year survival rates in older transplant recipients are comparable to those in their younger counterparts. Five year survival rates in older transplant recipients are worse due to excess cardiac, neurological, infective and neoplastic deaths (Zetterman *et al*., 1998; Varanasi *et al*., 1999). Incidentally, the incidence of organ rejection following transplantation has consistently been shown to be lower in older adults, possibly as a result of age-related immune dysfunction (James, 1997).

Although the scarcity of donor organs has inappropriately fostered the use of age as a prioritizing factor, the absence of significant differences in outcomes does not justify this practice in older patients who would otherwise qualify for liver transplantation.

Similarly, available data indicate that livers harvested from elderly donors (50–70 years) may be transplanted with reasonable success rates. However, eligible older donors must be carefully screened to avoid the risk of early postoperative liver dysfunction and compromised graft survival (Hoofnagle *et al*., 1996).

Key points

- Age-related pathophysiological changes include hepatic hypoperfusion, decreased hepatic mass, reduced activity of phase 1 hepatic drug-metabolizing enzymes, compromised hepatic regeneration, relative dilatation of the common bile duct and increased lithogenicity of bile. These changes result in enhanced vulnerability of the ageing hepatobiliary system to disease.
- Hepatobiliary diseases are a major cause of morbidity and mortality in older adults. The mortality rate from chronic liver disease in adults aged over 65 years is 3–6 times higher than that in middle-aged adults. Biliary disease is the leading indication for acute abdominal surgery in older adults. Older adults with viral hepatitis are more likely to develop complications such as fulminant hepatic failure, liver cirrhosis and hepatocellular carcinoma
- Twenty percent of all patients diagnosed with autoimmune hepatitis are over the age of 65 years. Drug-induced hepatitis is more common in older adults due to multiple factors including increased exposure to drugs, compromised hepatic metabolism and increased risk of hepatotoxicity with the use of certain drugs in older adults.
- Older adults are more likely to present with atypical features of biliary tract disease, and life-threatening complications such as gallbladder perforation and emphysematous cholecystitis. Emergency biliary surgery has worse outcomes in older adults. The risks of expectant therapy in older adults with asymptomatic biliary tract disease must be weighed against the benefits of elective intervention.
- Advanced age is not an absolute contraindication to liver transplantation. Quality of life, morbidity and one-year survival rates in older transplant recipients are comparable to those in their younger counterparts.

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CHAPTER 24

Sphincter function

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Introduction

Faecal incontinence is a common condition which affects up to 21% of community-dwelling elderly individuals over the age of 65 years,[1–3] and prevalence in the institutionalized elderly exceeds 50%.[4,5] An acute diarrhoea can result in an incontinence episode even in healthy people, when the rectal reservoir is overwhelmed by liquid/loose stools. Patients with faecal incontinence experience anxiety, fear of embarrassment, emotionally and socially devastating silent suffering, isolation and depression.[6] Faecal incontinence, along with urinary incontinence, is among the leading reasons for nursing home placement.[7]

Anatomy and physiology of the anal canal and rectum

In order to understand better the clinical presentation, evaluation and treatment options for faecal incontinence, the anatomy and physiology of the anal canal and rectum are briefly reviewed along with changes that occur with ageing.

The *rectum* is a tubular structure, 12–15 cm in length, with the anal canal extending about 4 cm, from the anal verge to the anorectal ring. The anal canal is separated by a dentate line into an upper mucosal lining and lower cutaneous segment. The area above the dentate line is supplied by the sympathetic and parasympathetic systems, whereas below the dentate line the somatic nervous system provides innervation. Just above the dentate line there are 8–12 rectal columns (anal cushions) with their bases connected to each other. The high-pressure zone of the anal sphincter is formed by the combination of muscles (internal anal, external anal and the puborectalis) and anal cushions.[8,9]

The *internal anal sphincter* is a circular muscle layer that starts from the rectum. The internal anal sphincter is tonically contracted at rest, preventing the involuntary loss of stool and gas.

Tone of the anal sphincter

The internal anal sphincter contributes 50–85% of the resting tone of the sphincter with the external anal sphincter contributing 25–30%, the remaining 15% coming from the anal cushions.[10–12] In response to rectal distension, the internal anal sphincter tone increases initially, followed by decreased tone constituting the anorectal inhibitory response.[8]

Changes with ageing

The thickness of the internal anal sphincter increases with age, as confirmed by ultrasound and magnetic resonance imaging.[13–15] The functional significance of this change is unclear. It could be a compensatory change for the maintenance of continence,[12] but this is unlikely, as the age-related changes in anal sphincter pressures are modest in healthy individuals.[16,17] The most likely explanation is increased connective tissue or 'sclerosis' of the internal anal sphincter with ageing.[18]

The *external anal sphincter* is a striated muscle surrounding the inner smooth muscle and terminating distal to the internal anal sphincter. Both the puborectalis and the external anal sphincter provide voluntary control of continence in response to various stimuli such as the increased intra-abdominal pressure that occurs with coughing, rectal distension and anal dilatation.[9,19] Voluntary anal sphincter pressure decreases with age and the pressure is lower in women than in men.[20]

The levator ani muscle is a major component of the pelvic floor and is composed predominantly of three striated muscles: iliococcygeus, pubococcygeous and puborectalis. The puborectalis muscle plays the largest role in continence and is a U-shaped loop of striated muscle slinging around the posterior aspect of the external anal sphincter, pulling the anal canal forwards creating the anorectal angle (Figure 24.1). The puborectalis and resultant anorectal

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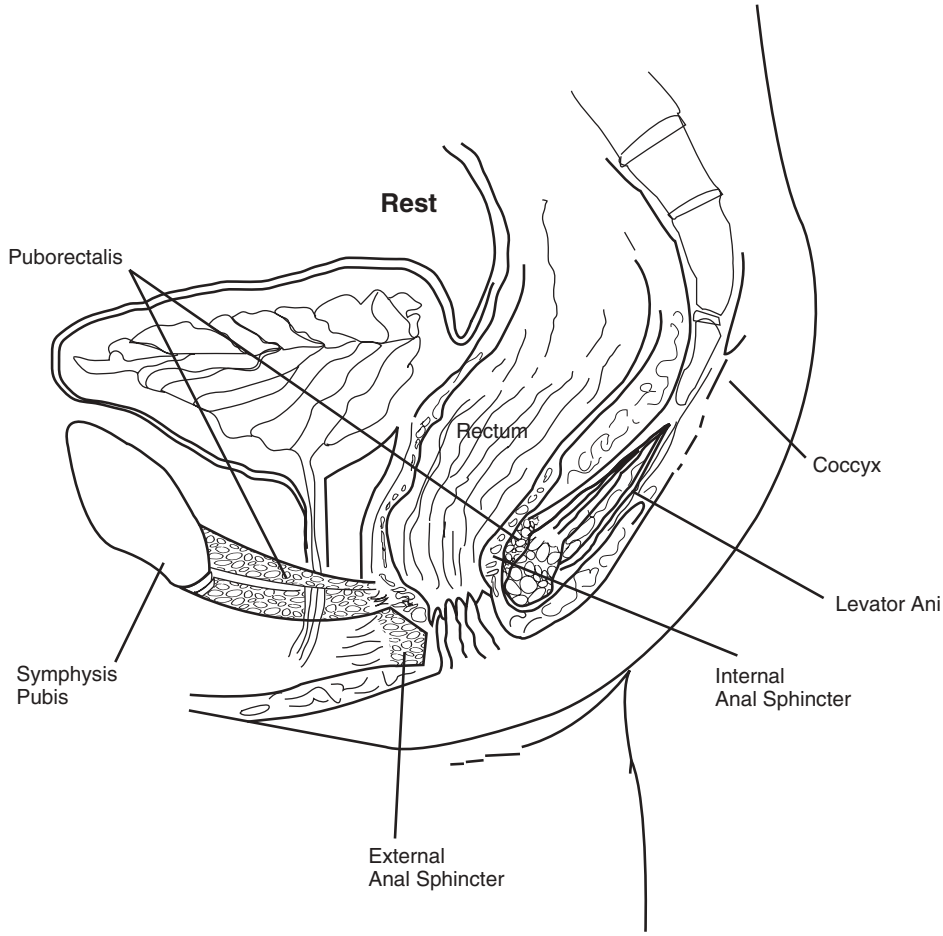

Figure 24.1 Anatomy of the anorectum at rest.

angle aid in the maintenance of continence, as this angle becomes more acute with voluntary sphincter contraction, providing an anatomical obstruction to the distal movement of stool retained above the angle.[21]

Physiology of defecation

Both the sensory and motor neurons of the anorectum interact to maintain continence and control the process of defecation. The desire to defecate is usually preceded by propagation of contractions in the proximal colon, resulting in the movement of faeces into the rectum with relaxation of the distal colon/rectum, relaxation of the internal anal sphincter and contraction of the external anal sphincter until the socially appropriate time for defecation.[22,23] The sensory receptors in the anal canal determine the nature of luminal contents, that is, whether the contents are solid, liquid or gas.[24] When voluntary defecation is desired, the intra-abdominal pressure rises due to abdominal wall contraction. The muscles of the pelvic floor (external anal sphincter, puborectalis and other muscles of the levator ani) relax. Relaxation of the puborectalis results in straightening of the anorectal angle, providing a straightened conduit for stool movement (Figure 24.2). The anal canal relaxes with the increased rectal pressure, resulting in the evacuation of stool.

Mechanism of continence

Continence is maintained through the combined action of the external and internal anal sphincters and the puborectalis muscle. Determinants of continence include resting anal tone, resistance to opening at the anus, rectal compliance, normal anorectal sensation and the consistency of stools.[25] In addition, mobility and intact cognition are required in order to have a controlled bowel movement. Impairment in any of these mechanisms may result in faecal incontinence.

Prevalence and importance

The prevalence of faecal incontinence in the general population is reported to be 2.2%,[26] but the study referred to did

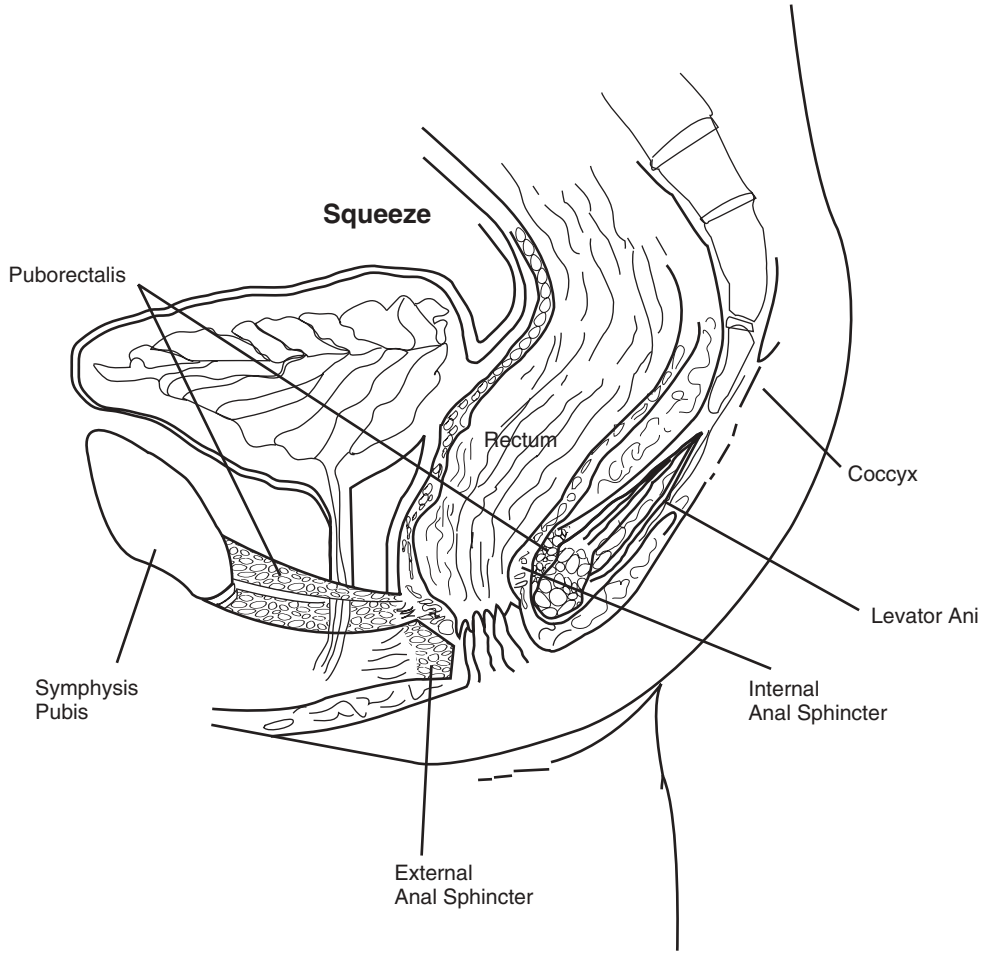

Figure 24.2 Anatomy of the anorectum during squeeze.

not include individuals residing in nursing homes. When individuals over the age of 65 years were studied, the frequency of faecal incontinence increased from 3.7 to 27% (Table 24.1). The greatest prevalence of faecal incontinence is found in nursing homes, with more than 50% of long-term care residents affected by chronic faecal incontinence.[5] A higher prevalence of faecal incontinence is seen in geriatric hospital wards (20–32%) and geriatric psychiatry patients (up to 56%),[28,29] and 80% of patients hospitalized with dementia also experienced faecal incontinence.[10] Double incontinence (i.e. faecal incontinence and urinary incontinence) occurs 12 times more commonly than faecal incontinence alone, with 50–70% of patients with urinary incontinence also suffering from faecal incontinence.[28–30] This is not surprising, as the combination of urinary and faecal incontinence is the second most common cause of institutionalization of elderly persons.[31]

Faecal incontinence is a marker for poorer overall health and is associated with increased mortality.[4,32] Incontinent nursing home residents experience more urinary tract infections and pressure ulcers.[33] The total health care costs attributable to faecal incontinence are difficult to determine as few studies have examined healthcare costs for faecal incontinence alone. Most healthcare cost information comes from nursing homes caring for patients with faecal incontinence, urinary continence or both. The nursing home-related costs for incontinence were $3.26 billion in 1987 and the yearly cost of adult diapers alone is $400 million.[34,35] The additional health expenditure reaches in excess of $9000 per patient-year of incontinence.[33]

Risk factors and causes of faecal incontinence

The risks and causes of faecal incontinence are summarized in Table 24.2. Risk factors for faecal incontinence include a prior history of urinary incontinence, the presence of neurological or psychiatric disease, poor mobility, age greater than 70 years and dementia.[25,36] Possibly the most common predisposing condition to faecal incontinence is faecal impaction, which is reported in up to 42% of elderly patients admitted to geriatric units.[37] These patients are

Table 24.1 Prevalence of faecal incontinence.

Country	Authors	Prevalence in general population (%)[a]	Prevalence in persons aged >65 years (%)[a]
New Zealand	Campbell *et al.*[1]	–	3.1
Switzerland	Faltin *et al.*[90]	4.4[b]	–
Germany	Giebel *et al.*[91]	5	–
The Netherlands	Kok *et al.*[2]	2.3	4.2–16.9
Japan	Nakanishi *et al.*[32]	–	8.7 M; 6.6 F
USA (Wisconsin)	Nelson *et al.*[27]	2.2	–
USA (Boston)	Resnick *et al.*[92]	–	17
USA (Minnesota)	Roberts *et al.*[93]	8.3 M; 13.1 F	17 M; 27 F[c]
USA (Minnesota)	Talley *et al.*[94]	–	3.7
France[d]	Chassagne *et al.*[4]	–	58
USA (Wisconsin)[d]	Nelson *et al.*[7]	–	47
England[d]	Peet *et al.*[95]	–	20.8

[a] M = male, F = female.
[b] Only women studies.
[c] Age >50 years.
[d] Studies reporting prevalence in long-term care.

Table 24.2 Risk factors and causes of faecal incontinence.

Risk factors[23,27]
Prior history of urinary incontinence
Presence of neurological disease
Presence of psychiatric disease
Poor mobility
Age >70 years
Dementia
Causes of faecal incontinence[36]
A Faecal impaction
B Loss of normal continence mechanism
  1 Local neuronal damage (e.g. pudendal nerve)
  2 Impaired neurological control
  3 Anorectal trauma/sphincter disruption
C Problems overwhelming normal continence mechanism
D Psychological and behavioural problems
  1 Severe depression
  2 Dementia
  3 Cerebrovascular disease
E Neoplasm (rare)

often chronically constipated resulting in incontinence from leakage around the large faecal impaction. The problem is further complicated by the presence of decreased rectal sensation, allowing the progressive accumulation of stool in the rectum.[38] Faecal incontinence in diabetes mellitus occurs from autonomic neuropathy and is exacerbated in the presence of diabetic diarrhoea.[39] Pelvic neuropathy may result from prolonged straining and birth trauma. Faecal incontinence results in these patients because of sphincter damage and pudendal neuropathy.[40] Trauma to the anal canal such as anal surgery, including haemorrhoidectomy, anal fissure repair and anal dilatation, may disrupt the anal sphincter muscles, resulting in impaired continence.[41,42] Patients with total internal sphincterotomy have a 40% risk of faecal incontinence, while partial sphincterotomy carries a risk of 8–15%.[43–45]

Clinical subgroups

There are three main types of faecal incontinence: (a) overflow (b) reservoir and (c) rectosphincteric. Overflow incontinence is specially seen in cognitively impaired, bedridden nursing home individuals and the risk factors are outlined in Table 24.3. Reservoir incontinence is seen in individuals with diminished colonic or rectal capacity. This condition is commonly seen with radiation proctopathy, rectal ischaemia, idiopathic inflammatory bowel disease and proctocolectomy with ileoanal anastomosis. Rectosphincteric incontinence is seen in conditions associated with structural damage to one or both anal sphincters, pudendal neuropathy affecting the external anal sphincter and or puborectalis muscle and/or rectal sensation, or degenerative or myogenic disorders affecting the internal or external anal sphincter.

Evaluation of faecal incontinence

The goals in evaluating faecal incontinence include establishing the severity of incontinence, understanding

Table 24.3 Risk factors for overflow incontinence.

Inadequate fibre
Inadequate water intake
Immobility
Inadequate toileting facilities
Mental status changes
Metabolic abnormalities
Hypothyroidism
Hypercalcaemia
Medication
Narcotics
Antipsychotics
Antidepressants
Calcium channel blockers
Diuretics

Table 24.4 Evaluation of faecal incontinence.

A. History
Chronic medical condition
Diabetes and chronic diarrhoea or constipation
Cerebrovascular accidents or cord compression
Dementia and depression
Immobility
Trauma during childbirth
Surgery history
Haemorrhoidectomy
Sphincterotomy
Fistulectomy
Colon resection and dilatation
Radiation to the prostate or cervix for carcinoma
Review of medications such as antipsychotic, sorbitol-based medications (theophylline)
B. Physical examination
Saint Louis University Mental Status Examination or Mini-Mental State Examination
Geriatric depression scale
Neurological examination
Rectal examination

the pathophysiology present and directing the patient to appropriate therapy for their condition. This is accomplished through history, physical examination and investigations targeted at determining the aetiology of faecal incontinence.

History and physical examination

The physician may find it difficult to recognize faecal incontinence since patients usually will not volunteer information about incontinence unless asked. This information is best elicited through direct questioning regarding bowel habit and continence. It is helpful to identify when the symptoms first occurred, and to determine if the patient has any sensations such as the passage of stool or gas, fullness in the rectum or warning symptoms such as abdominal cramps and urgency. Inquiry about the home environment may reveal barriers to bathroom facilities, especially in nursing homes and particularly in patients with walkers. Table 24.4 summarizes important areas to address during history. Colitis of any cause may result in loose stools that overwhelm the continence mechanisms. In the evaluation of faecal incontinence, several components of the neurological history deserve attention. A cerebrovascular accident may limit the patient's physical ability to use the toileting facility. The new onset of faecal incontinence may also herald the presence of cord compression, especially when associated with other neurological symptoms.

A thorough review of prescription and over-the-counter medicines and supplements may reveal an underlying cause for the altered bowel habit. Medicines causing diarrhoea include magnesium-containing antacids and poorly absorbed sugars such as sorbitol and mannitol (used in dietetic products). Sorbitol is also frequently used as a base in elixirs, for example, theophylline elixir. The intentional or inadvertent use of cathartics may contribute to diarrhoea and incontinence.

The physical examination helps to identify the pathophysiology of faecal incontinence and can guide the ordering of appropriate tests for further evaluation.[46] The usual physical examination may be supplemented by a Mini-Mental Status Examination or Saint Louis University Mental Status Examination, which help identify patients with cognition problems.[47,48] The neurological examination includes assessment of general patient mobility, motor strength and sensory testing. The 'anal wink' is elicited by stroking the skin lateral to the anal canal and observing the contraction. Absence of this reflex suggests significant neural damage. Anal gaping can be seen when the buttocks are parted in patients with paraplegia.[49] The perineum should be inspected for dermatitis, haemorrhoids, fistula, surgical scars, skin tags, rectal prolapse, soiling and ballooning of the perineum (suggesting weakness of the pelvic floor). Following inspection, the next step is digital rectal examination to note the baseline sphincter tone, squeeze pressure, any asymmetry of the sphincter on squeeze and the amount and character of the stool (hard pellets or soft). The positive predictive value of digital examination is 67% for detecting decreased anal tone when compared with anal manometry.[50] Patients with high or normal sphincter tone can also be incontinent, especially in the setting of large rectal volumes or altered rectal sensation. In patients with lesions of the spinal cord or cauda equina, the sphincter tone may be normal, but when pressure is applied to any part of the anorectal ring the phenomena of gaping can be seen. Findings in the normal elderly patient typically reveal lower anal canal pressures.[51]

Diagnostic tests

A number of tests are available to provide data on colonic and anorectal function.[52] Table 24.5 outlines most of the tests necessary for the investigation of faecal incontinence. In the elderly population, the most important thing is to exclude faecal impaction. Even in the absence of stool in the rectal vault, higher impaction may be present. If the patient is at risk, a plain abdominal radiograph is required to exclude high impaction. A flexible sigmoidoscopy or colonoscopy examines the colorectal mucosa for evidence of colitis, neoplasia, inflammatory bowel disease, colonic and rectal ischaemia, laxative abuse and other structural abnormalities. Anorectal manometry provides comprehensive information regarding anorectal function as it quantifies anal sphincter tone and assesses anorectal sensory responses, the anorectal inhibitory reflex and rectal compliance.[53] Anorectal manometry either provides new information or confirms the suspected diagnosis in patients with faecal incontinence.[54] A finding of decreased rectal compliance may point to faecal incontinence from increased stress on the continence mechanism as the stool is received in the rectum (i.e. a stiff rectum does not accommodate the stool bolus, resulting in overflow).[55] Electromyography measures the neuromuscular integrity between the distal portion of the pudendal nerve and the anal sphincter muscle.[56] Electromyography correlates well with anorectal manometry but its use in the routine assessment of faecal incontinence is controversial.[52,57] Anal ultrasound defines the internal and external anal sphincters.[58] Anal ultrasound can be used to identify isolated sphincter defects, present in about two-thirds of incontinent patients.[59,60] Ultrasonographic findings correlate with both surgical and electromyographic findings.[61,62] Magnetic resonance imaging (MRI) has also been used to evaluate the sphincter defects, with definition superior to anal ultrasound as it provides higher spatial resolution and better contrast for lesion characterization.[63] Endoscopic ultrasound (EUS) allows the identification of perianal disease such as fistula and abscess and assessment of sphincter integrity in faecal incontinence.

Treatment

The treatment of faecal incontinence depends on the underlying aetiology and severity of the incontinence.

Table 24.5 Diagnostic tests for faecal incontinence.

Plain abdominal X-ray
Sigmoidoscopy/colonoscopy
Anorectal manometry
Electromyography
Anal ultrasound or magnetic resonance imaging (MRI)
Endoscopic ultrasound (EUS)

Table 24.6 Summary of treatment options.

Conservative
Redirection in persons with cognitive impairment
Habit training
Adding fibre to the diet except when inflammation is present
Prompt voiding
Kegel exercise
Antidiarrhoeal agents (once infection is excluded)
Biofeedback
Surgical (few or no data on older persons)
Sphincter repair
Neosphincter operation
Alternative therapy
Artificial anal sphincter implantation
Injection of glutaraldehyde
Sacral nerve stimulation
Colostomy

Table 24.6 summarizes the main treatment options for faecal incontinence. Minor degrees of faecal incontinence can be treated conservatively, whereas patients with severe faecal incontinence require more aggressive treatment. Overflow incontinence treatment options include disimpaction, bowel cleansing and habit training. Treatment options for reservoir incontinence include a reduction in dietary fibre, treatment of underlying inflammation, use of loperamide and colostomy in severe cases.

Patients with mental impairment such as dementia may simply need to be directed to the toilet or reminded of its use. Physical limitations and environment obstacles need to be addressed if these are contributing to incontinence, as they can often be overcome by simple measures. Habit training involves a regular schedule of defecation, usually after breakfast, often incorporating the use of supplemental fibre and regularly scheduled enemas when defecation is delayed more than 2 days. Habit training is particularly effective for patients with overflow incontinence.[64] It has been shown that prompted voiding increases the number of continent bowel movements and reduces number of incontinent bowel movements; this study was designed primarily for urine incontinence.[64] Sphincter training exercises ('Kegel' exercises) alone do not increase the number of continent episodes.[65] In diabetic patients where gut dysmotility is suspected, clonidine may be used. Topical application is preferred over the oral preparation. A trial of cholestyramine may be helpful if bile acid malabsorption is suspected. Antidiarrhoeals such as loperamide are helpful when the stool is loose.[66] A double-blind crossover study of 30 patients receiving loperamide, codeine or diphenoxylate with atropine for 4 weeks found

that all reduced the stool frequency but loperamide and codeine were more effective in reducing faecal incontinence compared with diphenoxylate.[67] Diphenoxylate and codeine have more central nervous system side effects than loperamide and are generally best avoided in the elderly in this setting.

Biofeedback is classically described as a learning theory with operant conditioning as its theoretical basis, and was first described by Engel *et al*.[68] Biofeedback is a non-surgical, non-invasive, relatively inexpensive outpatient method of treating faecal incontinence.[69] Biofeedback for faecal incontinence involves improving the strength of the external sphincter and improving anorectal sensation.[65] Biofeedback provides immediate and long-term improvement of faecal incontinence.[70] Biofeedback training teaches the patient to recognize small volumes of rectal distension and to contract the external anal sphincter while simultaneously keeping the intra-abdominal pressure low. This is accomplished by measuring the anal canal pressure, showing this to the patient on a visual display and providing verbal feedback. Table 24.7 shows the success rate, age range and number of sessions involved in different studies. Better results are achieved when treating motivated, mentally capable patients. Patients should also have some degree of rectal sensation and be able to contract the external anal sphincter.[71] Miner *et al*. compared active sensory biofeedback with sham retraining.[72] In the active group, biofeedback training reduced incontinent episodes by 80% per week in this study, whereas the control group showed no change from the baseline. This improvement lasted over 2 years in 73% of patients available for follow-up. Geriatric patients with limited mobility who had faecal incontinence were treated initially for faecal impaction but 13 of them continued to be incontinent. These patients were then treated with biofeedback, which improved sphincter strength and reduced incontinence episodes by more than 75%.[65] A review of biofeedback showed improved continence in 13 of 14 studies.[73] In a review of 46 studies involving the use of biofeedback for faecal incontinence in 1364 patients (76% female), less than 20% of these studies included randomization and most involved relatively small numbers of subjects. Improvement in continence occurred in at least half of the patients. No specific details regarding age-related differences were noted.[74]

Surgical therapy

Surgical intervention is generally considered when more conservative measures have failed in patients with severe incontinence and identifiable anatomical defects. Although surgery is more commonly recommended in younger patients, the appropriately selected elderly patient fairs well with surgical intervention.[75]

Sphincter repair

In the setting of an isolated sphincter defect, especially anterior sphincteroplasty is very successful[76,77] Three basic approaches have been described: direct apposition, overlapping anterior sphincteroplasty and plication procedures (anterior, posterior and total pelvic floor repair). An improvement in anal function was reported, demonstrated by anal manometry before and after anterior sphincter repair.[78] There was a 96% improvement in anal function compared with preoperative symptoms (all women aged 22–75 years, mean age 37.8 years). The outcome of surgical repair is variable as some patients may continue to have incontinence and others develop new bowel problems postoperatively.[79]

Neosphincter operations

Muscle transposition may be considered for severe faecal incontinence where standard therapy has failed. Techniques include graciloplasty, dynamic graciloplasty and gluteus maximus transposition. The results of graciloplasty vary significantly.[80–82] The result of graciloplasty is improved by electrical stimulation after the implantation of electrical electrodes and a pulse generator.[83] Electrical stimulation provides the gracilis muscle with the properties to function as a sphincter.[84] In a prospective multicentre trial, 66% of patients with graciloplasty achieved continence in a follow-up at 2 years.[85] The performance of graciloplasty in the elderly has not been reported.

Alternative therapies

Newer techniques have been developed for the treatment of faecal incontinence, but these procedures are described predominantly in younger age groups. A multicentre prospective trial was carried out in 12 patients who had failed conventional management for severe faecal incontinence and had an artificial anal sphincter implanted.[86] A successful outcome was achieved in 75% of the patients with a mean age of 33 years. This surgical technique has not been specifically applied to the elderly.

Injections of glutaraldehyde cross-linked collagen are simple and well tolerated for patients who do not respond to conservative therapy and have a surgically incorrectable problem (internal sphincter dysfunction). Of 17 patients (mean age 53 years) who participated in a study, 65% had symptomatic improvement, 12% had minimal improvement and 18% had no improvement.[87]

Sacral nerve stimulation for faecal incontinence has been shown to improve faecal continence along with improved quality of life in selected patients.[88] In a non-randomized study, the application of radiofrequency energy to the sphincter improved continence and quality of life.[89] Finally, for severe faecal incontinence when all the other

Table 24.7 Technical details and results of biofeedback therapy[a].

Authors	*N*	Age range (mean)	Control group	Biofeedback modality	Outcome measure	Improved	Follow-up duration (mean) (months)
Miner *et al.*[72]	25	17–76	Yes Randomized	Strength Sensory Coordination	Stool diary	77% BF 42% sham	24
Whitehead *et al.*[65]	18	65–92 (73)	Yes Randomized	Strength Sensory Coordination	Diary ≥75% improvement	77% 50% 42%	Post BF 6 12
Guillemot *et al.*[96]	24 16 BF 8 control	39–72 (60)	Yes Not randomized Patients chose therapy	Strength	Clinical score	75% 19%	6 24–36 (30)
Loening-Baucke *et al.*[97]	17 8 BF 9 medical therapy	35–84 (64)	Yes Not randomized Coordination	Strength Sensory	Stool diary ≥75% improved	50%[b] 38%[b]	3 12
MacLeod[98]	50	25–76 (55)	No	Strength	≥90% decrease in FI frequency	72%	12
Rao *et al.*[99]	22	15–78 (50)	No	Strength Sensory Coordination	Diary/VAS FI severity scale	≥75% = 53% ≥50% = 100%	12
Goldenberg *et al.*[100]	12	12–78	No	Strength	Not described	83%	3–24
Wald[69]	17	10–79 (48)	No	Strength Sensory Coordination	Interview Questionnaire ≥75% improvement	71%	2–38 (15)
Sangwan *et al.*[101]	28	30–74 (52.9)	No	Strength Sensory	Manometry Excellent or good results	75%	4–47 (21)
Glia *et al.*[102]	26	32–82 (61 median)	No	Strength Sensory	FI questionnaire ≥50% reduction FI	64%	12–48 (21)
Chiairioni *et al.*[103]	14	24–75 (49)	No	Strength	Diary cards ≥75% reduction FI Monthly interviews ×5 Then Q 3 months	75%	3–21 (15)
Cerulli *et al.*[104]	50	5–97 (46)	No	Strength Sensory Coordination	≥90% reduction FI	72%	4–108 (32)

Berti Riboli *et al.*[105]	21	14–84 (60)	No	Strength Sensory Coordination	≥90% reduction FI	86%	1.5 or 3
Patankar *et al.*[106]	72	34–87 (70)	No	Strength	Questionnaire ≥75% improvement Subjective satisfaction	85%	Not stated
Rieger *et al.*[41]	30	29–85 (68 median)	No	Strength	VAS	27%	1.5
					Incontinence score	23%	6
					>80% improved = cure	12	
					23%		
					any improvement	67%	
Ryn *et al.*[107]	37	22–82 (61 median)	No	Strength	FI score	59% good or very good	12–59 (44)
					Subject rating	41% some improved	
					VAS		
Buser and Miner[108]	13	13–66	No	Strength Sensory Coordination	Manometry Resolution of FI	92%	16–30
Norton and Kamm[109]	100	14–82 (49 median)	No	Strength	Bowel diary	43% (cure)	End of BF
				Sensory	Symptom questionnaire	24% (improved)	
				Coordination			
Ko *et al.*[110]	25	31–82 (63)	No	Strength Coordination	Symptom improvement No. of FI episodes	92%	7
Leroi *et al.*[111]	27	29–74 (53)	No	Strength Sensory Coordination	Clinical improvement Good vs poor	30%	Not reported

[a]FI = faecal incontinence, VAS = visual analogue scale, BF = biofeedback.
[b]Unchanged from controls.

procedures failed, a diverting colostomy is usually the surgical procedure of choice.

Conclusion

Faecal incontinence is a common problem in the elderly population, particularly affecting individuals in the community and nursing homes. In addition to the inconvenience of the incontinence for the patient and caregiver, it is a marker of poor health and associated increased mortality. Patients and their caregivers must be questioned specifically about the presence of faecal incontinence and its severity. All patients with faecal incontinence warrant an initial medical evaluation, including the exclusion of faecal impaction by rectal examination and X-ray film of the abdomen. Cognitively impaired patients benefit most from habit training. Several surgical procedures are available and may be helpful in selected older persons in selected centres. Future studies are needed to identify which patients will obtain the most benefit from these interventions and to determine the most cost-effective evaluation and treatment regimens in the ageing population.

Key points

- Faecal incontinence is a common problem that is often not reported to the physician.
- In persons with faecal incontinence, faecal impaction should always be excluded.
- In healthy elderly with faecal incontinence, anal manometry and biofeedback should be utilized.
- Anal ultrasound can also be used to identify a defect suitable for treatment with sphincteroplasty.
- Common causes of faecal incontinence include cognitive impairment and faecal impaction.

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CHAPTER 25

Constipation

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Defining constipation

Constipation most classically refers to reduced defecation frequency and hard stools. Physicians typically define constipation as less than three bowel movements per week. Patients more frequently describe constipation as defecatory difficulty with predominant complaints of straining or hard stools. This holds particularly true in older adults. Understanding the patient's view of 'constipation' assists in the evaluation and treatment process.

The normal defecatory process requires sufficient cognition recognizing the need to defecate, normal colon transit and normal pelvic floor function. Normal colon transit ranges from 24 to 72 h. Defecation is most often preceded by high-amplitude propagated colonic contractions. These colonic contractions occur in response to meals, particularly those with higher concentrations of calories and fat. Colonic motility is also more robust during waking hours and quiescent at sleep. Once stool is delivered to the rectum, defecation may be voluntarily initiated through a set of coordinated actions. First the stool bolus must be sensed through local sensory neurons and recognized centrally. Initiation of the defecation may follow with relaxation of the puborectalis muscle, opening of the anorectal angle and relaxation of the anal sphincters and accompanied by a simultaneous rise in intra-abdominal pressure (Figure 25.1). An abnormality affecting any of these areas results in the development of an altered bowel pattern (Table 25.1).

Constipation may be defined in many different ways. Simply stated, primary constipation refers to constipation without an obvious cause and secondary constipation results from external aetiologies. These external causes of altered bowel function may include neuromuscular disorders, metabolic abnormalities, medications, insufficient diet or mechanical factors obstructing the movement of stool. Constipation may be further defined as acute or chronic. Chronic constipation indicates that symptoms have been present for more than 3 months and typically dates back years. Acute constipation requires a more rapid investigation into the aetiology, including evaluation for structural abnormalities or recent medication changes. Patients with chronic constipation may initially be treated symptomatically with fibre and/or simple laxatives. Those not responding to usual treatments require further investigation to evaluate for evidence of slow transit constipation or dyssynergic defecation (also called pelvic outlet dysfunction). Although constipation commonly occurs in the setting of the irritable bowel syndrome (IBS), new-onset IBS occurs less frequently in older than in younger patients. Specific criteria have been defined for identifying constipation by different investigators. The most commonly used are the Rome criteria, now in their third iteration, a classification used primarily for the purpose of clinical trials.[1]

Epidemiology, pathophysiology and impact

Constipation has long been misunderstood as a common problem associated with ageing. The prevalence of self-reported constipation, physician visits and laxative use increases with ageing.[2–4] In contrast, reported stool frequency does not change with age.[2,3] Challenges in defining the prevalence of constipation in elders relates to the variety of criteria used in different studies. Self-reported constipation affects 27% of individuals aged 65 years and older, whereas only 17% of elders meet more stringent (e.g. Rome criteria) diagnostic criteria for constipation.[5] When adjusting for race and laxative use, odds ratios for less than three bowel movements per week in individuals aged 70–79 and $\geq$80 years were 0.61 [95% confidence interval (CI), 0.51–0.72] and 0.85 (95% CI, 0.68–1.03), respectively, compared with individuals <40 years of age.[2] Thus, age alone is not an independent risk factor for reduced stool frequency. Likewise, little evidence exists to support low-fibre diets, lack of fluid or reduced exercise as contributing to constipation in the otherwise healthy older patient.[6,7]

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

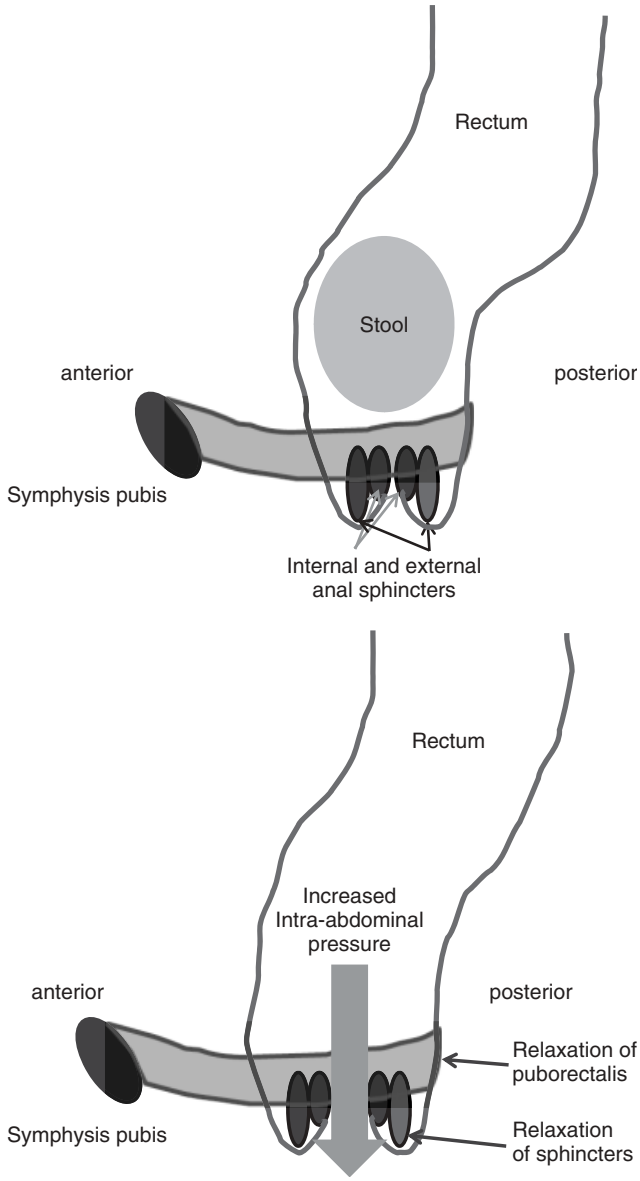

Figure 25.1 Illustration of the defecatory process.

Women report fewer bowel movements per week than do men. Non-whites and individuals of lower socioeconomic status report fewer stools.[8] In frail elders, up to 45% report constipation as a health concern.[9] The prevalence of constipation is higher in nursing home residents, a finding partially explained by the use of constipating medications.[10] Nursing home residents frequently (58%) use laxatives, usually on an as-needed basis.[11] In older persons, the development of constipation typically represents the effects of medications and/or comorbid disease. The traditional perception of constipation as a result of ageing no longer holds; the healthy older person is not predestined to develop constipation.

Table 25.1 Anatomical distribution of changes associated with constipation.

Central nervous system
Awareness of need to defecate
Cerebrovascular accident
Dementia
Peripheral nervous system
Controls myogenic activity of puborectalis
Pudendal nerve injury
Enteric nervous system
Controls rectal sensory function, peristalsis and internal anal sphincter
Parkinson's disease
Desensitization (chronically distended rectum)
Diabetes mellitus
Skeletal muscle
Contraction/relaxation of puborectalis and external sphincter
Direct muscular damage (e.g. prior birth trauma, sphincterotomy)
Rheumatological disorders (e.g. scleroderma, reduced muscular strength)
Incoordination
Idiopathic
Parkinson's disease
Cerebrovascular accident

Elders reporting constipation more often describe straining and hard bowel movements than reduced stool frequency.[2,12,13] Population-based prevalence of constipation includes 40% of community-dwelling adults over the age of 64 years.[14] The risk factor most commonly reported for constipation is medication use, including non-steroidal anti-inflammatory drugs (NSAIDs).[14]

Despite the lack of difference in risk factor-adjusted constipation rates between elders and younger individuals, elders more frequently use laxatives. Up to 50% of elderly women reporting use laxatives. Overall, 20–30% of community-dwelling elders use laxatives on at least a weekly basis. In nursing homes, 58% of residents receive laxatives on at least an intermittent basis.[11] Few economic studies in the USA have outlined the costs of laxative use by elders. Annual estimated healthcare costs using an administrative claims database (excluding out-of-pocket costs) were $7522 per person (average age 52 years) at one health maintenance organization.[15] Most elders self-treat with over-the-counter products; hence the economic impact of laxative use is probably considerably higher than this estimate.

The findings of similar stool frequency but increased defecatory difficulty parallel the reported physiological changes that occur in the digestive tract with ageing. Colon transit overall is generally well preserved with ageing in humans.[16] Changes in pelvic floor function may contribute to defecatory difficulty, with older women demonstrating reduced opening of the anorectal angle and a greater degree

of perineal descent compared with younger women.[17] Pudendal neuropathy also occurs more commonly with ageing and may negatively affect pelvic floor function.[18] Other factors correlated with constipation in ageing include reduced caloric intake, use of multiple medications, haemorrhoids and pain in the abdomen.[19,20] Many diseases that occur more commonly in elders also contribute to the development of constipation, such as diabetes mellitus, Parkinson's disease and stroke.[21–23] Prior surgery may also affect bowel function in elders. In women over 50 years of age, hysterectomy results in prolonged colon transit time and greater complaints of constipation and straining than in controls.[24] Since ageing alone has little influence on the development of constipation, when complaints of constipation occur in elders, it commonly relates to medical comorbidities and increased defecatory difficulty.

The consequences of constipation in elders make it a significant health problem. The presence of chronic constipation impacts functioning in daily living, and elders with these complaints rate their health lower than people without gastrointestinal symptoms.[25] These findings were not confounded by the presence of other chronic illnesses or medication use. Health-related quality of life is reduced in patients with chronic constipation.[26] The presence of constipation has also been hypothesized to increase urinary tract symptoms with treatment of constipation resulting in reduced urinary frequency, urgency and dysuria.[27] Constipation is also associated with bowel incontinence and treatment of constipation reduces incontinence episodes.[28,29] Immobile or cognitively impaired individuals with constipation face an increased risk of faecal impaction and stercoral ulceration.[28,30] Constipation reduces quality of life and diminishes self-perceived health in community-dwelling elders.[25] More effective strategies are needed for reducing the burden of illness and costs associated with constipation.

Aetiology of constipation

Of the multiple causes of constipation in older persons, most relate to medication use or coexisting medical illness (Tables 25.2 and 25.3). The most commonly implicated medications are opiates, NSAIDs and medications with anticholinergic effects. Although immobility and reduced fluid and fibre intake are often implicated in the development of constipation, there is little evidence to support this folklore. Increased physical activity does not reliably improve constipation.[31] Reduced caloric intake correlates more closely with constipation in elders than do differences in fibre intake.[19] Likewise, reduced liquid intake does not appear to cause constipation in most elders.[13] Increased psychological distress correlates with reports of constipation by elders, although the mechanism for this association remains unknown.[13,19]

Table 25.2 Medications commonly associated with constipation.

Anticonvulsants
Antidepressants (SSRIs and TCAs)[a1]
Antihistamines
Antipsychotics
Bromocriptine
Calcium channel blockers
Calcium supplements
Diuretics
Ferrous gluconate and ferrous sulfate
Levodopa
Non-steroidal anti-inflammatory drugs
Opiates

[a] SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Table 25.3 Medical conditions commonly associated with constipation.

Mechanical obstruction
Colonic neoplasia
Colonic stricture (intrinsic or extrinsic)
Anal stenosis
Metabolic
Amyloidosis
Chronic kidney disease
Diabetes mellitus
Electrolyte disturbance (hypercalcaemia, hypomagnesaemia)
Hyperparathyroidism
Hypothyroidism
Neurological
Autonomic neuropathy
Cerebrovascular accident
Dementia
Multiple sclerosis
Parkinson's disease
Rheumatological
Polymyositis
Scleroderma
Psychiatric
Depression

Clinical approach

History

The evaluation of constipation begins first with understanding the patient's perspective on their altered bowel function and the time course of constipation development. The acute or subacute onset of constipation requires a more aggressive diagnostic approach to exclude structural lesions, including colon neoplasia, stricture and volvulus. Likewise, the presence of weight loss, rectal bleeding,

history of inflammatory bowel disease, family history of colorectal neoplasia or presence of iron deficiency anaemia require a structural examination to exclude cancer or other aetiology. Additional helpful details in the patient history include onset of constipation, frequency of bowel movements, sensation of incomplete evacuation, straining to defecate, consistency of the stool, associated abdominal pain, the need for digitation, perineal splinting or unusual postures for defecation to occur, episodes of bowel incontinence, prior abdominal or pelvic surgery, prior abdominal or pelvic radiation therapy and prior pregnancies. It is also necessary to review current medications and supplements, current and previously used laxatives with their degree of effectiveness, use of enemas and use of complementary therapies to treat constipation (e.g. high colonics, herbs, teas). Dietary history includes a general survey of calories ingested, fibre intake and restricted foods. Given the consistent association of constipation with depression and anxiety, a brief psychological assessment is also warranted. In general, the ideal, evidence based approach to the diagnostic evaluation of constipation remains to be identified.

Physical examination

The physical examination is directed to identifying underlying medical causes for constipation, excluding faecal impaction, and providing a preliminary assessment of anorectal function. A faecal mass may be palpable on abdominal palpation. Rectal examination includes inspection of the perineum at rest and with strain. Normal perineal descent during strain is 1–4 cm. No perineal descent suggests failure of the pelvic floor to relax and allow the passage of stool. Excessive perineal descent, sometimes characterized as a ballooning of the perineum, indicates excess laxity to the pelvic floor musculature and dyssynergic defecation. This finding is most common in multiparous women. The strength of the anal sphincter muscle at rest and with squeeze is assessed. Puborectalis and anal sphincter relaxation during strain provide a measure of proper of the appropriateness of pelvic floor function. Failure of relaxation or very high anal sphincter resting pressure suggests dyssynergic defecation. The presence of weak anal sphincter pressures may place the patient at risk for incontinence during treatment of the constipation. Rectal prolapse can be associated with difficult evacuation due to blockage of the anal canal with rectum. These patients usually also described episodes of bowel incontinence. A more severe rectal prolapse can be identified during strain in the left lateral decubitus position. A better way to assess for rectal prolapse is to have the patient strain over a commode. The examiner places a gloved hand below the anus and can feel the rectal prolapse descend and touch the glove. The degree of rectal prolapse can be assessed by visual inspection. The physical examination, including rectal examination. is a necessary part of the evaluation of any constipated patient.

Diagnostic tests

Laboratory tests often recommended in the evaluation of constipation include a complete blood count, metabolic panel that includes electrolytes, creatinine, magnesium and calcium and sTSH (sensitive thyroid-stimulating hormone). Stool examination for occult blood should be assessed. The need for a colonic structural examination is dictated by the need for routine colorectal screening, presence of worrisome signs such as bleeding or anaemia or recent change in bowel habit. The yield of colonoscopy in identifying neoplasia is no different in the individual with constipation compared to what would be identified in an asymptomatic population undergoing screening. Many patients with long-standing constipation and no warning symptoms can undergo a therapeutic trial with fibre or an osmotic laxative, preserving further evaluation for those who fail to respond to simple interventions.

Patients with more severe or medication-unresponsive constipation may benefit from further evaluation, including physiological testing. It is difficult to predict the underlying pathophysiology of chronic constipation by symptoms alone.[32] The presence of slow transit constipation or dyssynergic defecation may be suspected by a poor response to a trial of supplemental fibre.[33] Additional tests include colon transit measurement, colonic manometry, anorectal manometry, balloon expulsion testing and defecography. Colonic transit measurements may be performed scintigraphically or using radiopaque markers and plain abdominal radiographs. In practice, few centres have scintigraphy readily available. A variety of techniques have been described for measuring colonic transit using radiopaque markers, some providing data on regional colon transit. Since treatments have not yet been identified for treating regional colonic abnormalities, total colon transit measurements suffice. The 5-day colon transit measurement involves ingestion of a commercially available capsule containing 24 radiopaque markers (Sitzmark) and performing a plain abdominal radiograph 5 days later).[34] Transit is considered prolonged when five or more markers remain (Figure 25.2). Although markers remaining predominantly in the rectum suggest dyssynergic defecation or outlet dysfunction, the distribution pattern of the markers throughout the colon does not reliably differentiate between primary slow transit versus colon transit delayed as a result of outlet dysfunction (i.e. dyssynergic defecation).

Dyssynergic defecation refers to physiological difficulty with the rectal evacuation process. Synonyms include pelvic outlet dysfunction, pelvic floor dysfunction, anismus and paradoxical puborectalis contraction. Uncommonly, difficult rectal evacuation may be due to an anal stricture,

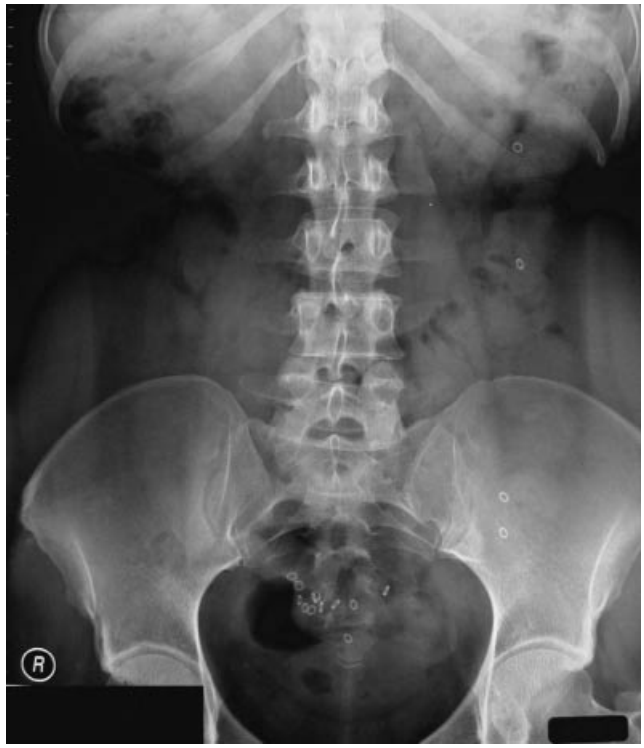

Figure 25.2 An abdominal radiograph obtained 5 days after ingestion of a capsule containing 24 radiopaque (small circles) markers. The presence of 16/24 markers on day 5 indicates the presence of slow colonic transit. The majority of the markers reside in the rectum with a few markers scattered in the sigmoid and descending colon.

obstructing rectocele or internal intussusception. The last two findings are most often the result of abnormal straining, rather than a primary problem themselves. The presence of dyssynergic defecation can be evaluated by anorectal manometry, electromyography of the anal sphincter, balloon defecation and defecography. Anorectal manometry involves measuring the pressures of the anal sphincter with a manometric probe in response to different manoeuvres, including straining. During strain, a rise in intra-rectal pressure should occur and the anal sphincter should relax. The presence of a paradoxical increase in sphincter pressure suggests the possibility of dyssynergic defecation. False positives occur at least 10% of the time with all tests of pelvic floor function. Therefore, two tests that independently confirm the same findings are required to make a secure diagnosis of dyssynergic defecation. Balloon expulsion testing is performed by placing a small balloon in the rectum and filling the balloon with 50–60 ml of warm water. The patient is asked to sit on a commode and expel the balloon. Normal expulsion occurs in 60 s or less. A prolonged time or failure to expel the balloon suggests dyssynergic defecation.[35] Anorectal manometry and balloon expulsion testing are the most commonly performed tests to identify dyssynergic defecation. Electromyography will also assess for proper anal sphincter muscle relaxation and contraction. The need to place needles in the anal sphincter has made this technique less attractive for most patients. Defecography involves placing a paste in the rectum. The patient sites on a commode and radiographs are obtained during defecation. Defecography assesses the opening of the anorectal angle and provides an assessment of sphincter opening, perineal descent and rectal emptying. Defecography typically is reserved for cases where an underlying structural abnormality is suspected or when other tests for dyssynergic defecation are equivocal. Additional physiological tests of colon transit and pelvic floor function are required in only the subset of patients refractory to medical management. Even in this highly selected group of patients, an abnormality is identified only 50% of the time.[36] Patients with refractory symptoms and normal physiological studies are defined as having 'normal transit constipation'. Many of these patients meet criteria for irritable bowel syndrome, particularly if their symptoms have been long-standing.

Treatment

The initial treatment strategy for constipation nearly always includes the ingestion of more dietary or supplemental fibre. Increased fibre intake improves stool consistency and accelerates colon transit in many individuals.[37] However, constipated elders actually consume more fibre at baseline than non-constipated controls.[38] Nonetheless, fibre generally provides a safe, inexpensive first-line approach. Increased fluid intake is also frequently recommended. Although this may have value in the dehydrated patient, increasing fluid intake in chronic constipation rarely improves constipation symptoms.[7] Likewise, increased physical activity is also recommended without clear evidence of efficacy.[7,39] General non-pharmacological advice given first line includes information about a normal bowel habit, ingestion of a healthy, fibre-rich diet and taking advantage of the meal-related increase in colonic motor activity. Given the strong association of constipation in older persons with medication use, elimination or adjustments should be made in medications, substituting less constipating alternatives where possible. Medications used in the treatment of constipation are listed in Table 25.4.

Pharmacological management

Bulking agents

Bulking agents commonly used include wheat or oat bran, psyllium, calcium polycarbophil, carboxymethylcellulose and partially hydrolyzed guar gum. There have been few high-quality randomized controlled studies assessing the

Table 25.4 Medications used in the treatment of constipation.

Agent	Daily dose
Bulking agents	
Bran (wheat or oat)	4–10 g (generally $\frac{1}{4}$ –$\frac{1}{2}$ cup)
Calcium polycarbophil	2–4 g
Hydrolyzed guar gum	3–6 g
Methylcellulose	2–4 g
Psyllium	3–6 g
Osmotic	
Lactulose	10–40 g
Magnesium salts	Generally avoided in elders
Sorbitol 70% solution	15–60 ml
Polyethylene glycol (PEG)	17–34 g
Stimulant	
Aloe	Safety/efficacy not established
Senna	15–30 mg
Bisacodyl	5–10 mg
Other	
Lubiprostone	8–24μ g b.i.d.
Probiotics	*Bifidobacterium infantis* 1 capsule daily
	Yogurt 8–16 oz daily
Methylnaltrexone	Weight-based dosing

efficacy of these agents. Studies with psyllium generally show improved stool form and frequency.[40,41] Studies assessing the efficacy of wheat bran, oat bran, calcium polycarbophil, carboxymethylcellulose and partially hydrolyzed guar gum are inadequate for assessing the efficacy of these agents. Fibre supplements may result in increased gas or bloating. This effect may be minimized by gradually increasing the dose of fibre. The effect of the fibre supplement may take 2–4 days before the patient sees results.

Stool softeners

Stool softeners such as dioctyl sodium sulfosuccinate (Colace) or dioctyl calcium sulfosuccinate (Surfak) are reported to soften the stool, easing defecation. Despite the widespread use of these agents, there are no randomized controlled trials showing efficacy. One study comparing dioctyl sodium sulfosuccinate with placebo showed no improvement in stool frequency or consistency.[42] Another study comparing dioctyl sodium sulfosuccinate with psyllium found psyllium to be superior.[43] The therapeutic use of stool softeners appears limited for the treatment of chronic constipation.

Osmotic laxatives

Osmotic laxatives improve stool form and bowel movement frequency by increasing the amount of water retained in the lumen of the gut. Polyethylene glycol (PEG) and lactulose have therapeutic value in the treatment of constipation. Other osmotic laxatives include sorbitol, magnesium salts and saline salts. PEG, lactulose and sorbitol have the greatest safety margins. Use of saline or magnesium salts comes with a risk for significant electrolyte disturbance, especially in older persons. Elders with normal renal function may become hypermagnesaemic with chronic use, especially at higher doses.[44] Magnesium salts should not be used in renal disease and saline salts should be avoided in chronic renal failure, end-stage liver disease and heart failure. PEG appears to be the best tolerated overall in elders. Lactulose and sorbitol undergo bacterial metabolism in the gut, leading to increased symptoms of bloating, abdominal cramping and flatulence in some patients, limiting their tolerability.

Several randomized, placebo-controlled trials of PEG showed efficacy in the treatment of chronic constipation. Compared with placebo, PEG improves stool consistency and stool frequency.[45] One study compared PEG with lactulose, showing improved efficacy with PEG and fewer side effects.[46] No studies using PEG directly assessed efficacy in older adults. One study in adults with a mean age of 45 years showed efficacy, safety and few side effects over a 6 month period with an isosmotic PEG electrolyte solution.[47]

Lactulose improves stool frequency and consistency with a success rate of 80% compared with a placebo response of 60%.[48] A study of nursing home residents with constipation compared lactulose with a glucose solution. Lactulose improved stool frequency, reduced the need for enemas and reduced faecal impaction over a 12 week period.[49] The difference in number of faecal impactions between the two groups was an astounding difference of six for lactulose versus 66 for glucose. A literature review revealed no placebo-controlled randomized trials assessing the primary efficacy of sorbitol in the treatment of constipation. One randomized comparative trial of lactulose and sorbitol in elders found no difference in laxative effect and no strong preference for one laxative over the other by the study subjects.[50] Abdominal symptoms were similar between the two groups except for greater complaints of nausea in the lactulose group. The cost of sorbitol is generally less than that of lactulose, making it the preferred agent for many patients.

Magnesium hydroxide is the most commonly used magnesium-containing osmotic laxative. Despite the fairly widespread use of this laxative, there are no high-quality studies demonstrating efficacy and safety in treating constipation. Nonetheless, magnesium intake is well known to cause diarrhoea, supporting its use in the treatment of constipation. Magnesium salt intake in normal subjects results in a linear increase in stool weight with a 7.3 g increase in faecal weight for every millimole increase in stool magnesium.[51] A cross-over

study comparing magnesium hydroxide and 8.7 g of a bulk laxative in geriatric long-stay patients showed increased stool frequency in the magnesium hydroxide group.[52] Magnesium salts must be used with caution in older patients with consideration given for periodic monitoring of serum magnesium levels in those taking magnesium-containing laxatives chronically. The use of sodium-containing laxatives has not been well studied in the treatment of constipation. Sodium-containing laxatives are better absorbed systemically than magnesium-containing laxatives. When oral Phospho-soda was used as a colonic preparation for diagnostic examination, significant changes in electrolytes occurred.[53] Even in the setting of a normal creatinine, an age-related increase in phosphate occurred.[53] Sodium-containing laxatives cannot currently be recommended for the routine treatment of constipation in older persons.

Stimulant laxatives

The adverse effects that stimulant laxatives have in the treatment of constipation remain one of the most steadfast medical myths.[7] Stimulant laxatives have been reported to damage the colon and cause laxative dependence. This perception may relate to the occurrence of melanosis coli, a dark brownish discoloration of the colon that occurs with long-term use. The presence of melanosis coli has no functional significance. Prior studies reporting damage to the colonic enteric nerves and smooth muscle were anecdotal and uncontrolled. It is likely that many of these patients had pre-existing abnormalities of the colon. When used at recommended doses, stimulant laxatives are unlikely to harm the colon. Stimulant laxatives result in abdominal discomfort and electrolyte imbalance in some patients.[54]

No high-quality, placebo-controlled studies have assessed the efficacy of stimulant laxatives in the treatment of chronic constipation. Most commonly available stimulant laxatives include the anthraquinones, diphenylmethane derivatives and ricinoleic acid. Anthraquinone laxatives include senna-containing products and aloe. An observational (uncontrolled and not blinded) study using a senna-containing concentrate as part of a programme that included a stool softener and increased fibre and fluid intake resulted in improved bowel evacuation in 86% and prevented faecal impaction in nursing home patients with constipation.[55] Compared with placebo, bisacodyl 10 mg daily for 3 days increased stool frequency, improved stool form and reduced straining in adults with constipation.[56] A comparison of bisacodyl with sodium picosulfate (uncontrolled) showed improvement with both in about three-quarters of subjects.[57] Stimulant laxatives are typically reserved for patients who do not respond to other laxatives. They are widely available without a prescription and are frequently used.

Prokinetic agents

There are no currently available FDA-approved prokinetic agents for use in chronic constipation. Tegaserod, a $5HT_4$ agonist, improves the symptoms of constipation in adults.[58] Data regarding efficacy in individuals over the age of 65 years have not been reported. Tegaserod was removed from the market due to a *post hoc* analysis showing an increased occurrence of ischaemic events with tegaserod compared with placebo. Neostigmine, an acetylcholinesterase inhibitor, produces prompt colonic decompression. The use of neostigmine is reserved for hospitalized patients with acute colonic pseudo-obstruction.[59]

Chloride channel agonist

Lubiprostone selectively activates chloride C-2 channels to increase intestinal fluid secretion. Lubiprostone does not affect colonic motility or sensation in humans. Patients reported more spontaneous bowel movements with lubiprostone compared with placebo (six versus four per week, $p = 0.001$) with the majority of patients experiencing a bowel movement within the first 24 h.[60] The main side effect seen with lubiprostone was nausea. This effect is mitigated when the medication is taken with a meal and appears to be less problematic in elders.

Opioid antagonists

Opiate pain medications are well known to cause constipation. A peripheral mu opioid antagonist reverses opiate-induced constipation without affecting the analgesic effects or causing withdrawal symptoms.[61,62] This medication is administered subcutaneously every other day using a weight-based dosing. The response can be rapid with a median time to first bowel movement of 30 min. Alvimopan, also a mu opioid antagonist, has been studied in postoperative ileus with good results. It has not been approved for use in chronic constipation and currently is only used in the hospital setting. For elderly patients with chronic constipation due to opiates, future development of peripheral opiate antagonists shows promise. Methylnaltrexone use is appropriate for opiate-induced constipation that has not responded to other measures.

Miscellaneous agents

Misoprostol, a prostaglandin agonist, stimulates intestinal secretion and intestinal transit. Its use is limited by the common occurrence of side effects, including abdominal pain and cramping.[63] Its use is reserved for patients with refractory constipation. Colchicine, well known for causing diarrhoea in the acute treatment of gout, may be used in patients refractory to other medications.[64] Colchicine frequently causes increased symptoms of abdominal pain, limiting its use. Glycerine suppositories have long been used as an over-the-counter agent for stimulating

bowel movements. The medical literature is lacking in assessments of their effectiveness. Linaclotide increased cyclic guanosine monophosphate, stimulating chloride and bicarbonate secretion. Published phase 2 trials showed a dose-dependent improvement in stool frequency.[65] Phase 3 trials have been completed but this agent has not yet undergone FDA approval.

Enemas

The use of enemas in the treatment of constipation is typically limited to the acute situation. There is no medical evidence to support the routine use of phosphate enemas in the treatment of constipation.[66] The use of phosphate enemas is well described to cause serious hyperphosphataemia, especially in patients with renal insufficiency.[67] Any enema must be used with caution owing to the risk of colonic perforation.[68] Soap suds enemas should not be used. Small-volume tap water enemas may be helpful in emptying the rectum. Larger volume tap water enemas may be used on occasion, but even these can result in hyponatraemia.[69] In patients with very refractory constipation, the use of antegrade enemas has been described.[70,71] Antegrade enemas involve creating a caecostomy placed surgically or endoscopically. Water or PEG is flushed through the tube periodically to facilitate colonic emptying. No high-quality, controlled trials have assessed any of these enema therapies.

Special categories of constipation

Medication use is strongly correlated with the development of constipation in older persons. Where possible, unnecessary medications should be discontinued and necessary medications switched to a less constipating alternative when one is available. For example, verapamil causes more constipation than other calcium channel blockers. Chronic opiate use results in constipation in up to 50% of individuals.[72] Methadone and fentanyl may be less constipating than other morphine derivatives.[73,74] Methylnaltrexone, a peripheral mu opioid receptor antagonist, improves oral caecal transit and induces laxation without inducing opiate withdrawal symptoms.[75] Opiates potently slow gastrointestinal transit and allow enhanced intestinal absorption of fluid. A rational approach involves outlining a strategy to prevent constipation at the initiation of opiate use. There have been no high-quality studies to indicate the best strategy. As noted previously, methylnaltrexone improved stool frequency in opiate-induced constipation. It is typically reserved for patients with more refractory symptoms as it is administered by injection every other day. PEG improved stool form in methadone-induced constipation.[76] Stimulant laxatives are also commonly used for opiate-induced constipation.

Constipation commonly occurs in Parkinson's disease related to dyssynergic defecation from incoordination of the pelvic floor musculature during defecation and the constipating effect of medication used to treat Parkinson's disease. Psyllium has been used successfully to treat constipation in these patients.[77] Individuals with dementia frequently develop constipation. Sorbitol and lactulose have been reported to be successful in an observational study.[78]

The use of combinations of laxatives has rarely been addressed in the literature but is commonly encountered in practice when a single agent is ineffective. The most common combination is an osmotic laxative with a stimulant laxative. In patients with continued complaints of constipation despite the use of a single laxative, obtaining a plain abdominal radiograph to assess the degree of stool retention may be helpful. Patients with a large amount of stool (and no evidence of faecal impaction) may be treated with a colon preparation such as balanced electrolytes plus PEG (e.g. NuLYTELY) to cleanse the colon. The patient may be then started on an osmotic laxative with a stimulant laxative available on an as-needed basis every 2–3 days if a satisfactory bowel movement does not occur. Patients without significant stool loading should be assessed for the presence of irritable bowel syndrome. About 11% of elders have symptoms consistent with irritable bowel syndrome.[25] Patients with irritable bowel syndrome may benefit from medications directed at neuromodulation, although caution must be used due to the anticholinergic effects of many of these agents.[79]

Patients with refractory constipation and slow transit constipation benefit from subtotal colectomy and ileorectostomy.[80] Fortunately, this is rarely required as nearly 90% of patients with slow transit constipation respond to laxatives.[81] When dyssynergic defecation is present, biofeedback improves defecatory function in ~70% of patients.[82] Patients with both slow transit constipation and dyssynergic defecation should first be treated with biofeedback. When slow transit constipation persists after successful treatment of dyssynergic defecation, subtotal colectomy may be considered. Surgical therapy is most successful in patients without upper gut motility disorders or significant psychological symptoms.[83]

The optimal treatment for faecal impaction is not clear. Patients able to tolerate oral therapy may benefit from PEG or other osmotic laxatives with or without the use of enemas.[84] Patients with a hard or very large faecal bolus in the rectum may require manual removal of the faeces. Hyperosmotic, water-soluble contrast enemas have also been used with success in relieving faecal impaction.[85]

Conclusion

Complaints of constipation and use of laxatives remain common in older persons. When controlling for comorbidities, constipation is no more common in elderly than in younger persons. Stool frequency remains unchanged with

ageing. Elders more commonly complain of straining and hard stools. Risk factors for constipation include medication use, chronic medical illness and psychological distress. Healthy elders are no more likely to develop constipation that younger persons. Constipation adversely affects elders' sense of well-being and quality of life. The economic impact is also significant due to the cost of laxatives alone. In patients with up-to-date colorectal cancer screening who lack worrisome symptoms such as bleeding or weight loss, empirical treatment is appropriate with bulking agents or simple laxatives. Patients who fail to respond require a more detailed evaluation. Identifying the most effective treatment strategy for constipation in elders, whether in the community or long-term care setting, remains unclear due to the lack of high-quality therapeutic trials for most laxatives. Data support the use of psyllium, lactulose, sorbitol, PEG and lubiprostone in elders with constipation. The safest, best tolerated and least expensive laxatives (including the use of bulking agents) should be implemented first before prescribing the more expensive laxatives. Improved research in this area is needed to identify the most effective, economically viable therapeutic agents. New agents are just around the corner, providing more options for the treatment of constipation.

Key points

- Reports of constipation and use of laxatives are very common in older persons.
- Stool frequency is no different in elders compared with younger persons, with elders complaining most of straining and hard stools.
- The use of medications and chronic medical illnesses correlate more closely with the development of constipation in elders.
- Patients lacking worrisome symptoms may undergo an empirical therapeutic trial, reserving diagnostic testing for those who fail to respond.
- The best available evidence supports the use of psyllium, lubiprostone and osmotic laxatives (especially PEG) in the treatment of constipation in elders.
- Methylnaltrexone, available as an injection, is an important advance in the treatment of opiate-induced constipation.

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CHAPTER 26

Management of diarrhoea

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Overview of diarrhoeal illness

Although the definition of diarrhoea appears clear, there are specific parameters that need to be met prior to making a diagnosis. According to Gerding *et al.*,[1] there are three separate parameters which include new onset of >3 partially formed or watery stools over a 24 hour (h) period, ≥6 watery stools over 36 h or ≥8 unformed stools over 48 h. Once the diagnosis has been made, diarrhoea can be further classified as acute or chronic. Acute diarrhoea is diarrhoea lasting for 14 days or less. Persistent diarrhoea lasts for longer than 14 days. Chronic diarrhoea is diarrhoea lasting for longer than 1 month. The consequences of fluid and electrolyte loss are especially concerning for elderly adults. Furthermore, the management of diarrhoea can differ from the general adult population due to various comorbidities, living arrangements and inherent immune susceptibility that exist among elderly adults.

Diarrhoea is a common cause of death worldwide and one of the most common infectious illnesses in elderly nursing home patients.[2] This is particularly important in the treatment of the elderly as there is an inherent decline in immune defences which are often compounded by many close contacts derived from living in long-term care facilities. Once diarrhoea has been distinguished from incontinence and faecal impaction, one can further classify the type of diarrhoea. In addition, diarrhoea presenting with incontinence can represent a decompensation of existing poor gastrointestinal (GI) function in the elderly.[3] The subdivisions of acute and chronic diarrhoea can be further broken down into more categories according to the cause and presentation. Acute diarrhoea is usually infectious in nature, but can also be caused by medications, nutrition, diverticular disease and ischaemia.[3] Chronic diarrhoea can be further subclassified as secretory or watery, osmotic, fatty or bloody (inflammatory or exudative).[3]

Some elements of the GI tract, for example, immune function, change with age; a healthy ageing GI tract's absorptive capacity, mucosal anatomy and motility should be unchanged. Therefore, even in the elderly, the main goal in diarrhoeal management remains the identification of the aetiology of diarrhoea and preventing dehydration.

Acute diarrhoea

Infectious

Infectious diarrhoea is the most common cause of diarrhoea. The infectious causes of diarrhoea include viruses, bacteria and parasites.[2] The most common viruses include Norwalk virus, rotavirus and calicivirus. The bacteria include *Clostridium difficile, Clostridium perfringens, Campylobacter, Escherichia coli, Salmonella, Shigella, Staphylococcus* and *Vibrio*. Lastly, the parasites include *Giardia lamblia, Entamoeba histolytica, Cryptosporidium* and *Cyclospora*.[2,3]

C. difficile is the most common healthcare infection causing diarrhoea.[4] The organism is a spore-forming Gram-positive anaerobic bacillus with two exotoxins. Toxin A is an enterotoxin and toxin B is a cytotoxin. There are currently hypervirulent strains that are identified as B1, NAP1 and ribotype 027/toxinotype III. These hypervirulent strains produce 23 times more toxins A and B, which causes increased resistance to treatment.[5] Similarly to less virulent strains, they are associated with fluoroquinolone and cephalosporin use. The rate of *C. difficile* colonization in LTCF is 4–20% and outbreaks are severe.[6] In 1986, Bender *et al*. found 19 deaths from the 49 cases of infection in an outbreak in a Baltimore nursing home.[7] The outbreak lasted for 7 months despite precautions, antimicrobial use restrictions and treatment. *C. difficile*-associated disease (CDAD) is defined as diarrhoea, per previously defined criteria, pseudomembranes or stool toxin A or B or stool culture positive for toxin-producing *C. difficile* and no other recognized aetiology for diarrhoea.[1] Although the predominant presentation is with diarrhoea, ileus or absence of diarrhoea can occur in less than 1% of presentations. Therefore, with increased clinical suspicion, a toxin assay or culture must be performed on non-diarrhoeal stool. Some sources

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

estimate that >10% of hospitalized patients are colonized with *C. difficile*.[1] A history of treatment with antimicrobial or antineoplastic agents within the previous 8 weeks is present in virtually all patients, but is not included in the case definition to avoid bias and to allow comparison of antimicrobial use as a factor. In clinical practice, antimicrobial use is considered to be part of the operative CDAD definition. A response to specific therapy for CDAD is suggestive of the diagnosis and can be confirmatory.[1] Direct visualization using endoscopy detects pseudomembranes only 51–55% of the time.

CDAD is associated with proton pump inhibitor therapy (PPI). Akhtar and Shahee[8] studied the incidence and association of *C. difficile*-associated diarrhoea and PPI. The study found a significant association of *C. difficile* associated with antibiotics or chemotherapy [odds ratio (OR) = 2.3, 95% confidence interval (CI) = 1.5–3.7] and with PPI use (OR = 2.0, 95% CI = 1.6–2.6).

Brandt *et al*.[9] noted in 1999 that the response to treatment of CDAD was similar in groups less than and older than 60 years of age. In addition, the associated mortality between the groups was also the same. However, owing to the modest sample size of 89 CDAD patients in the study, there may have been insufficient statistical power to detect small yet meaningful differences. The older group was significantly more likely to have an elevated white blood cell count (>10 400 cells mm^{-3}) and nosocomial infection after >2 weeks of hospitalization. Both exposures from increased hospital stay or healthcare-associated contacts and also susceptibility may account for the increased rate of CDAD in the elderly.

The other bacterial and parasitic causes of diarrhoea and treatments are listed in Table 26.1. These infections can usually be distinguished by the type of diarrhoea, watery or bloody, or the time to diarrhoea onset. The invasive or inflammatory causes of diarrhoea include enteroinvasive *E. coli, Shigella* and *E. histolytica*. The Shiga-like toxin and Shiga toxin-producing organisms include *E. coli* and *Shigella*, respectively. While *E. coli* usually produces diseases at between 10 h and 6 days, *E. coli* O157:H7 can take up to 4 days to produce disease. *Shigella dysenteriae* can take up to 1 week to produce disease. *Salmonella, Yersinia enterocolitica* and *Campylobacter* produce disease 12–48 h after ingestion. Akhtar[2] reported a Maryland nursing home resident outbreak of *Salmonella* with a 24% rate of death in those affected.

Other infectious causes of diarrhoea are viruses, including Norwalk, Norwalk-like virus and rotavirus. These viruses are common causes of diarrhoea in the paediatric population. However, they have been noted to cause epidemic diarrhoea in the nursing home in The Netherlands[10] and Spain.[11] The viruses differ by the predominant time of year for presentation, with rotavirus causing disease during the cooler months. They are both acquired by the faecal–oral route; therefore, direct contact or contact with contaminated food and water is the most likely means of spread. A retrospective cohort study of nursing home residents and staff between December 1998 and January 1999 in the Rotterdam region found 107 attacks of acute onset diarrhoea or vomiting in the 120 residents and 102 staff members studied.[10] The resident gastroenteritis attack rate was 62% without any significant difference among number of room-mates or eating place. The study found that the nursing home staff contributed to the spread of illness. Those residents who were infected were older (77 versus 72 years, $p = 0.04$). In addition, the rate of attack increased with age, which was postulated to be related to mobility, intensity of nursing care and immune health.

Table 26.1 Infectious diarrhoea.

Pathogen	Medication/therapy
Bacteria	
Clostridium difficile	Metronidazole or vancomycin p.o.
Campylobacter jejuni	Erythromycin or azithromycin p.o.
Salmonella typhi	Ofloxacin or norfloxacin p.o.
Shigella	Trimethoprim–sulfamethoxazole or ofloxacin
Vibrio cholerae	Tetracycline
Parasitic protozoa	
Cryptosporidium parvum	Nitazoxanide p.o.
Entamoeba histolytica	Metronidazole then iodoquinol (diiodohydroxyquinoline) p.o.
Giardia lamblia	Metronidazole, furazolidone or nitazoxanide p.o.

Adapted from Refs 2 and 19.

Diagnosis of infectious diarrhoea should be guided by the initial presentation and history. Without fever, signs of dehydration, bleeding, abdominal pain or coexisting disease, supportive care without further testing can be appropriate.[2] However, the presence of the aforementioned symptoms and disease states or lack of resolution after supportive therapy for 48 h warrants further investigation. Depending on the clinical suspicion for *C. difficile*, stool toxin assays should be performed. In addition, in order to control disease dissemination, hand hygiene, barrier protection and environmental precautions (cleansing, disinfecting and disposables) are imperative. Specific antibiotic and antiparasitic treatment options for infectious causes of diarrhoea are included in Table 26.1.

Bloody

A common cause of lower GI bleed is diverticula. Diverticular colitis can be the cause of both chronic and acute diarrhoeal disease. It is believed the 60% of 80-year-olds have diverticulosis. Estimates indicate that 10–30% of GI

bleeds are from diverticula.[12] Bleeding is caused by non-circumferential rupture of the underlying vasa rectum.[12] In addition, the most common life-threatening bleeds are lower GI diverticular bleeds. Risk factors of diverticular bleeds include hypertension, anticoagulation, diabetes mellitus and ischaemic heart disease.[12] Bloody diarrhoea also occurs with ischaemic colitis, which will be considered in the next section.

Specific treatment for bleeding diverticula includes vasopressin infusion, embolization and surgery. According to Lewis,[12] vasopressin infusion via angiogram is 36–90% effective in the initial treatment of diverticular bleeds and 22–71% in recurrent bleeding. In addition, the success rate for selective embolization was noted to be 71–90%, with a relatively lower rebleeding rate than vasopressin infusion at 15–20%.

Ischaemic

Ischaemic colitis usually presents with colicky lower abdominal pain, diarrhoea, vomiting or rectal bleeding.[13] The acute presentation is often abrupt onset of pain and bloody diarrhoea; however, the problem can also be chronic in nature. Lactic acidosis is the most common metabolic disorder. Mesenteric ischaemia includes various presentations, such as acute mesenteric ischaemia, chronic mesenteric ischaemia, non-occlusive mesenteric ischaemia, mesenteric venous thrombosis and colonic ischaemia. Ischaemic vulnerability occurs in the splenic flexure and the rectosigmoid. Both areas are often referred to as 'watershed areas' because they represent incomplete anastomosis of the marginal artery between the inferior mesenteric and superior mesenteric or hypogastric, respectively.[14] Causes are varied, from embolism and atherosclerotic changes to mesenteric vessels, hypovolaemia, vasculitis, trauma, radiation or disseminated intravascular coagulation,[15] and medications as noted in Table 26.2. Six factors that are significantly related to ischaemic colitis include age over 60 years, haemodialysis, hypertension, hypoalbuminaemia, diabetes mellitus and constipation-inducing medication.[16]

Cangemi and Picco[14] described high mortality associated with ischaemia because of delayed diagnosis in the elderly and noted the appropriate studies for accurate diagnosis. Angiography is the gold standard in the diagnosis of acute mesenteric ischaemia. Multidetector computed tomographic (CT) angiography is also an option, but does not provide a therapeutic option.

Treatment of ischaemic colitis includes supportive care, which encompasses intravenous fluid resuscitation, bowel rest, antibiotics and avoiding vasoconstrictive medication. Mesenteric angiography can be used for direct visualization and treatment with vasodilators such as papaverine or thrombolytics.[14] The treatment of choice for both acute and chronic mesenteric ischaemia is surgery, with independent predictors for surgical mortality including age over 70 years, diagnosis after 24 h and metabolic acidosis in acute ischaemia.[14] With treatment symptoms resolved in about 2 days, but without treatment the ischaemia can progress to necrosis and result in perforation and shock.[16]

Table 26.2 Causes of mesenteric ischaemia: medications.

Vasoconstrictors (digitalis)
Norepinephrine
Cocaine
Pseudoephedrine
Argot alkaloids
Oral contraceptives
Estrogens
Diuretics
Antihypertensives
Non-steroidal anti-inflammatory drugs
Meloxicam
Chemotherapeutic agents
Paclitaxel
Alosetron

Adapted from Ref. 16.

Tube feeding/medications

Diarrhoea is commonly reported when a patient receives tube feeding, but there is not necessarily a causal relationship.[17] Since enteral feeding contains the nutrient-rich environment appropriate for bacterial growth, contamination of the feed can be causative. Therefore, any reusable components of the enteral feeding, including bags and tubing, need proper cleaning between uses. In addition, the opened packages should be refrigerated.[17] Another cause of diarrhoea with feeding is the flow rate. The initiation of feeding alone can result in diarrhoea, so it is recommended that enteral feeding be started at a low rate and titrated to the nutritional supplemental goal. The type of feed also has implications in causing diarrhoea. Gavi *et al*.[17] noted that isotonic formulations appear to be better tolerated when started at full strength, but hypertonic or elemental formulae should be started at half strength and then titrated to full strength 24 h later.

Treatment of enteral feeding diarrhoea includes decreasing the flow rate, supplementing fibre or changing to a lactose-free formulation as an initial measure.[3] However, these measures often do not identify the true cause of the diarrhoea. It is important to remember that medications are often switched to liquid formulations once tube feeds are started. These formulations often contain sorbitol, which can be a cause of diarrhoea.[18] This should always be considered and investigated.

Common medications implicated in causing diarrhoea include sorbitol-containing medications, magnesium,

non-steroidal anti-inflammatory drugs (NSAIDs), H2 blockers, proton pump inhibitors, antineoplastics, antiretrovirals and antibiotics.[13] Selective discontinuation of medications can elucidate the offending medications when multiple causes are possible.

Supportive treatment

Supportive treatment to prevent dehydration is the first-line therapy in all acute diarrhoeas. The Centers for Disease Control (CDC) recommendations[14] for treatment of diarrhoea with dehydration include the use of fluid and electrolyte replacement with oral rehydration solutions (ORS). If oral replacement is possible, the use of Pedialyte, Gastrolyte or other commercially available solutions with electrolyte and glucose is recommended. This hydration is to be taken in small, frequent amounts. Treatment should be based on degree of dehydration determined from physical findings, vitals and urine output. Although opiate antimotility agents such as loperamide and diphenoxylate with atropine may decrease the volume, use can compound illness when diarrhoea is caused by a bacterium or bacterial toxin. Therefore, the use of these medications should be restricted to individuals without bloody or mucoid diarrhoea.[19] Other non-specific medications include clonidine and octreotide.[3] For mild to moderate fluid loss, ORS administration is calculated as 50–100 ml kg^{-1} body weight over 3–4 h and 120–240 ml ORS for each diarrhoeal episode. For severe fluid loss, lactated Ringer's solution or normal saline should be administered intravenously in boluses of 20 ml kg^{-1} body weight until perfusion and mental status improve, and then 100 ml kg^{-1} body weight ORS administered over 4 h or 5% dextrose–½ normal saline intravenously at twice maintenance fluid rates.[19] In addition, the CDC states that ongoing fluid loss has the same parameters as mild to moderate fluid loss. If oral therapy is not possible, alternative routes include nasogastric tube or intravenous administration of 5% dextrose–¼ normal saline with 20 mequiv. l^{-1} potassium chloride. Hydration in the elderly can be complicated by common medical problems such as heart failure and renal failure.

Chronic diarrhoea

Watery

A watery diarrhoea occurs from either secretory or osmotic mechanisms. Ingestion of solutes and sugars that are poorly absorbable can cause osmotic diarrhoea. Many of the solutes are used in laxative or antacid preparations, such as magnesium sulfate/hydroxide and citrate. In addition, sugars such as sorbitol and fructose, often found in sweets and food, can also cause osmotic-type diarrhoea. Lactase phlorizin hydrolase or lactase activity is noted to be lost by most people by the age of 20 years.[3] There is a mutation that allows persistent function of the hydrolase, but this also can declines with age. This mutation is found commonly in northern European genetic pools,[3] but the hydrolase decline and deficiency also predominate in certain racial and ethnic groups. Lactose is unable to be metabolized into an absorbable form. Surgical causes of osmotic diarrhoea often involve disruption of absorption that occurs with small bowel partial or complete resections, ischaemia or vagotomy. Short bowel or gut syndrome develops when only 2 m of small bowel is present for absorption.

The most common cause of chronic diarrhoea is secretory and the long differential of causes includes, but is not limited to, endocrinopathies, medications, microscopic colitis, bile acid malabsorption, motility disorder, diverticulitis, laxatives, idiopathic, vasculitis and neoplasia.[3] Endocrine causes of diarrhoea include diabetes, Addison disease, hyperthyroidism and tumours secreting gastrin, vasoactive intestinal peptide, catecholamines and adrenaline. Medications can be a direct cause of diarrhoea because of either drug interactions or decreased clearance.[3] Although neurological disruption or disorders can cause dysmotility, irritable bowel syndrome should still be considered in the elderly although it usually presents earlier in life.

One of the epidemic causes of idiopathic secretory diarrhoeas is Brainerd diarrhoea. Brainerd diarrhoea was named after a town in Minnesota where the first outbreak occurred in 1983. It is characterized by acute onset watery diarrhoea that lasts for 4 weeks or longer and in some reports up to years. It can occur sporadically or in outbreaks and often affects adults aged 41–65 years.[20] According to Vugia *et al*. in 2006, there have been nine outbreaks since 1985. The last published report was of an outbreak that occurred in late 1998 in Humboldt County, California.[20] There were 23 patients identified and the median age of the population was 64 years. The maximum duration median was 16.5 in 24 h and often included faecal urgency and incontinence. Of the 21 patients contacted after 6 months, 18 still had loose stools three or more times per day or were taking antidiarrhoeal medications. All of the patients received antidiarrhoeal medications and 13 received antibiotics. Further investigations have been made on the pathology of chronic watery diarrhoea. Bryant *et al*. described the histological changes in biopsy specimens of Brainerd diarrhoea specimens from an outbreak on a cruise ship to the Galapagos Islands.[21] The 12 small bowel biopsies were negative and the 20 patient colonic biopsies showed epithelial lymphocytosis, surface degenerative changes or thickened subepithelial collagen plates. The lymphocytosis was greater than in control samples of normal colon and with varied comparisons to various colitis (acute, ulcerative and collagenous) presentations. The exact aetiology and treatment of this chronic watery diarrhoea remain unknown.

Distinguishing secretory from osmotic diarrhoea is the first step with watery diarrhoea. While calculating an osmotic gap is usually considered useful in corroborating evidence for secretory or osmotic diarrhoea, some believe that it does not solely differentiate secretory from osmotic diarrhoea because of bacterial metabolism and possible elevated electrolytes in secretory diarrhoea.[22] An osmotic gap >125 with a pH <5.3 characterizes osmotic diarrhoea, while an osmotic gap <50 is usually found in secretory diarrhoea. Other tests can be effective in detecting carbohydrates such as a hydrogen breath test in lactose intolerance and testing for faecal reducing substances. Diagnosis of secretory diarrhoea includes exclusion of infection and structural disease, selective testing for endocrinopathies and secretory tumours and a cholestyramine trial to exclude bile acid diarrhoea.[3] Osmotic diarrhoea testing involves stool analysis for pH to detect carbohydrate malabsorption and magnesium levels to detect ingestion or laxative use.[3]

Inflammatory

Inflammatory bowel disease (IBD) mainly comprises Crohn's disease (CD) and ulcerative colitis (UC), but also includes microscopic colitis. Individuals 60 years of age and older comprise 10% of individuals with IBD.[23] In CD, the Montreal and Vienna classifications use age as a factor. In the Vienna classification, the age is stratified as either above or below 40 years of age. In the Montreal classification, there are three classifications: A1 below 16 years old, A2 between 17 and 40 years old and A3 above 40 years old.[24] Therefore, the population over 65 year of age is not specifically addressed in either classification. According to Picco and Cangemi, the disease presentation is similar in the age stratifications of before and after the age of 40 years.[23] However, the older age group appears to have a higher colonic only involvement than in the younger age group. Hospitalization and azothioprine use were lower after age 40 years, but overall surgical treatment appeared to be similar. In addition, after age 40 years, UC symptoms are believed to be less severe, with some atypical symptoms such as constipation and predominant proctocolitis versus colitis in younger patients. In addition, initial presentations are more severe.

According to Picco and Cangemi,[23] CD has shown survival differences in studies in which patients were followed for an extended period of time. Examples include a 21 year follow-up in Olmsted County, Minnesota, and a 54 year follow-up in Copenhagen, Denmark.[23] Although there may be a slightly increased mortality with CD among older individuals and with prolonged disease, the significance of age at the time of diagnosis has not been established.[23]

Microscopic colitis, including both lymphocytic colitis and collagenous colitis, is not uncommon in the elderly and the median age of onset is 68 years.[3] Unlike UC and CD, microscopic colitis does not usually present with haematochezia. According to Schiller,[3] the illness is secondary to luminal antigen causing an increase in lamina propria inflammatory cells and intraepithelial lymphocytes. Collagenous colitis is more common in women and accounts for up to 20% of chronic diarrhoeas in those older than 70 years.[23]

Inflammatory diarrhoea is established by the presence of faecal leucocytes. Faecal occult blood may also be present. Establishing the cause of inflammatory diarrhoea includes exclusion of structural disease with imaging or direct visualization and biopsy with sigmoidoscopy and colonoscopy for the colon or endoscopy for the small bowel.[3]

Acute treatment for both CD and UC includes reducing inflammation and treating infection with antibiotics. Chronic treatment includes immunomodulators, anti-inflammatory medications and surgery. The immunomodulators used include ciclosporin, infliximab, certolizumab, adalimumab, azathioprine, methotrexate and 6-mercaptopurine. The anti-inflammatory medications used include corticosteroids, mesalamine, sulfasalazine and 5-aminosalicylic acid. Specific difficulties with the treatment of older adults with IBD include side effects and the method of administration. The elderly often have pre-existing problems with continence, so retention of enemas or suppositories presents a unique challenge. Picco and Cangemi[23] noted that foam preparations have better retention qualities. In addition, the side effects of antibiotics such as metronidazole used in colonic CD can cause peripheral neuropathy and results in subsequent discontinuation. Corticosteroids used in both UC and CD can cause significant side effects such as osteoporosis, bone fractures, mental status change, diabetes and hypertension.[23] In addition, bone marrow suppression can occur with allopurinol when combined with azathioprine or 6-mercaptopurine. Whereas surgery can be curative for UC, remission or reduction or symptoms is the result with CD. In addition, surgery presents challenges such as possible ileostomy and malabsorption.

The treatment for microscopic colitis is different to that for UC and CD. UC and CD treatments have been used without significant data. However, in a systematic review, Chande *et al*.[25] reviewed the relevant data for induction of response, histological response and maintenance of response. For collagenous colitis, 10 randomized trials were studied which showed that budesonide resulted in significant induction and maintenance of clinical and histological response and was well tolerated. Although bismuth subsalicylate, prednisolone and mesalamine (with or without cholestyramine) showed possible evidence of effectiveness, *Boswellia serrata* extract and probiotics were not effective in the treatment of collagenous colitis according to the systematic review. Only three randomized controlled trials were reviewed

for lymphocytic colitis treatment. Budesonide also showed some evidence of induction of clinical and histological response and was well tolerated.

Steatorrhoea

Steatorrhoea is fatty diarrhoea resulting from malabsorption of dietary fat. This diarrhoea is characterized by bulky, foul-smelling stools that float. Some causes of malabsorption include pancreatic insufficiency, coeliac disease, bacterial overgrowth, cholestasis, CD, parasitic disease and Whipple disease. The most common causes are pancreatic insufficiency 30%, celiac disease 30% and bacterial overgrowth 20%.[25] Weight loss medications such as orlistat and fat substitutes such as olestra can also be causative. The signs of malabsorption can be subtle. Common symptoms include anorexia, bloating and excessive flatus. Fat malabsorption results in secondary nutrient deficiencies and systemic disease such as anaemia, hypoalbuminaemia, osteoporosis, cramps and paraesthesias.[25] In addition, these deficiencies can be an added burden in those with existing nutritional challenges.[3] Although the establishment of steatorrhoea is usually established by the gross characteristic faeces, a Sudan stain can be used to detect the presence of fat. In order to find the cause, structural disease must first be excluded with small bowel radiographs, CT scan or small bowel biopsy.[3] Once structural disease has been excluded, pancreatic insufficiency is ruled out with a secretin or cholecystokinin test, empirical trials of enzyme replacement therapy and stool chymotrypsin activity. The antigliadin immunoglobulins IgA and IgG and antiendomomysial IgA are particularly specific for coeliac sprue.

Conclusion

Diagnosis of acute and chronic diarrhoea should be guided by the initial presentation and history. Alarm symptoms including fever, bleeding, abdominal pain and haemodynamic instability are important in guiding both diagnosis and treatment. Although distinguishing diarrhoea by its most common acute and chronic presentations is helpful, it is always important to remember that the disease process can evolve over time. For example, the initial presentation of inflammatory bowel disease may cause a watery diarrhoea that may develop into a malabsorptive diarrhoea.

Key points

- Diagnosis of chronic and acute diarrhoea should be guided by the initial presentation and history.
- Alarm symptoms including fever, bleeding, abdominal pain and haemodynamic instability are important in guiding both diagnosis and treatment.
- Acute diarrhoea includes infectious, bloody and ischaemic types.
- Chronic diarrhoea includes watery, inflammatory and steatorrhoea types.

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CHAPTER 27

Diseases of the pancreas

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The ageing pancreas

The pancreas has considerable functional reserve so that any anatomical changes associated with age have little, if any, effect on pancreatic function. Morphological changes, however, do occur as part of the ageing process. Ectasia of the main pancreatic duct occurs, which can cause confusion in the interpretation of the appearances on endoscopic pancreatography. Additionally, ductal epithelial hyperplasia and intralobular fibrosis, which rarely lead to pancreatic atrophy, can occur. In an autopsy study of the elderly in the UK, ductal narrowing not due to strictures, space-occupying lesions due to the superior mesenteric artery, splenic artery, aorta, vertebral osteophytes, sympathetic ganglia and lymph nodes were noted. The study also showed metastases in the pancreas, which could be mistaken for primary pancreatic tumours. Finally, ageing can be associated with impaired pancreatic blood supply due to atherosclerosis.

Functional studies have been carried out on elderly patients and compared with those on younger patients. The volume of pancreatic secretion falls in the elderly, as do the outputs of lipase, trypsin and phospholipase.[1] There does not appear to be a corresponding fall in fat absorption. Changes are very variable in older persons, suggesting that disease processes such as arteriosclerosis and not ageing, *per se*, may be responsible for the small changes seen.

Inflammatory diseases of the pancreas

Acute pancreatitis

Although alcohol abuse is the major cause of acute pancreatitis in the middle aged, it is less common as a cause in the elderly. Acute pancreatitis, however, occurs with increasing frequency in the elderly because of an increased prevalence of gallstones. A recent English study showed that hospital admission rates for acute pancreatitis had doubled over a 30 year period in all age groups but the case fatality rates had not altered.[2] Hospital admissions for acute pancreatitis per 100 000 were 13 or more for both men and women over 65 years of age and the case fatality rates were 8 per 100 patients at 29 days after presentation and 7.4 at 30–364 days after presentation. Corresponding rates in the over-75 years old age group were even higher. In addition to alcohol and gallstones, other predisposing factors for acute pancreatitis in the elderly include hypercalcaemia (usually due to hyperparathyroidism), hypertriglyceridaemia and obstruction to pancreatic flow such as that caused by tumours, endoscopic pancreatography and uraemia. Acute pancreatitis occurs in up to 30% of patients following cardiac bypass surgery, perhaps because of the administration of large doses of intravenous calcium chloride. Acute pancreatitis is also associated with biliary sludge and cholecystectomy or endoscopic papillotomy may prevent recurrence. Elderly patients are more likely to be taking prescribed medication, but whether drugs are a major cause of acute pancreatitis is debatable. Most reports of drug-related pancreatitis are anecdotal and the potential severity of the disease precludes drug challenges. A large retrospective German study of acute pancreatitis implicated drugs as a possible cause in only 1.4% of the patients. The disease was mild and ran a benign course.[3] It is now recognized that autoimmune pancreatitis is not rare in older persons.[4] On imaging, it is characterized by pancreatic enlargement with an irregular narrow pancreatic duct. Histologically there is lymphoplasmacytic infiltrate with swirling fibrosis and obliterative phlebitis. The tissue stains positive for IgG4-positive cells. Serum levels of IgG4 are also elevated. It can be associated with biliary structures, retroperitoneal fibrosis, parotid infiltration and mediastinal lymphadenopathy. The condition is highly sensitive to steroid therapy.

Pathophysiology of acute pancreatitis

The basic underlying pathophysiological mechanism in acute pancreatitis is pancreatic duct obstruction. This allows autodigestion of the gland by its own enzymes. Reflux

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of bile and duodenal juices into the pancreatic duct are also important. In the majority of patients, the process is self-limiting but in some the disease becomes fulminating. This leads to pancreatic necrosis and activation of inflammatory cytokines, which can result in generalized organ failure (systemic inflammatory response syndrome). If the necrosed pancreas becomes infected by gut bacteria, the disease is often fatal.

Presentation of acute pancreatitis

The illness characteristically presents with severe abdominal pain, often leading to acute hospital admission. The pain usually occurs in the epigastrium and radiates through to the back and is often relieved by sitting forward. This presentation, however, may differ in the elderly when the illness may be confused with myocardial infarction or a perforated abdominal viscus.

The physical signs are those of an acute abdomen. Jaundice, vomiting, fever, tachycardia and hypotension may occur. If severe, haemorrhagic pancreatitis supervenes with retroperitoneal haemorrhage, which leads to bruising in the flanks (Grey Turner's sign), around the umbilicus (Cullen's sign) or even below the inguinal ligament (Fox's sign).

Diagnosis of acute pancreatitis

The diagnosis is supported by the finding of high levels of amylase in the serum. Elevated levels of serum lipase are more specific than elevated amylase levels. The serum lipase rises within 4–8 h, peaks at 24 h and returns to normal in 8–14 days.

Radiological examinations are increasingly important and sophisticated. Straight abdominal X-rays may show a sentinel loop – an area of small bowel ileus adjacent to the inflamed pancreas. In severe pancreatitis, the chest X-ray can reveal a pleural effusion, areas of atelectasis and pulmonary oedema. These appearances occur in patients of all ages.

Ultrasonography is important. Gallstones and dilated bile ducts suggest pancreatitis of biliary origin. Overlying gas shadows often impair visualization of the pancreas, but when seen, the gland appears swollen. Ultrasonography is important in detecting pancreatic pseudocyst and fluid collections within the abdomen. Enhanced computed tomography (CT scanning) is useful in showing evidence of pancreatic necrosis and localized fluid collections both in and outside the pancreas (Figure 27.1). CT scanning may also reveal gallstones and bile duct or pancreatic duct dilatation not obvious in ultrasound scanning. In selected patients, endoscopic retrograde cholangiopancreatography (ERCP) is useful in showing dilated bile ducts and gallbladder stones (Figure 27.2) and has the added advantage that bile duct stones can be cleared. When acute pancreatitis is diagnosed by these imaging methods, biochemical tests (serum levels of amylase and lipase) are elevated in over 90% of patients.

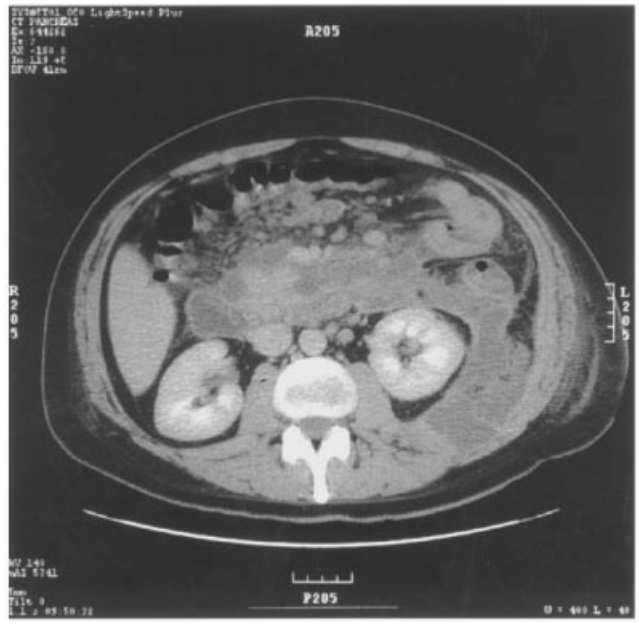

Figure 27.1 Acute pancreatitis with necrosis. Courtesy of Dr N. Al-Mohktar

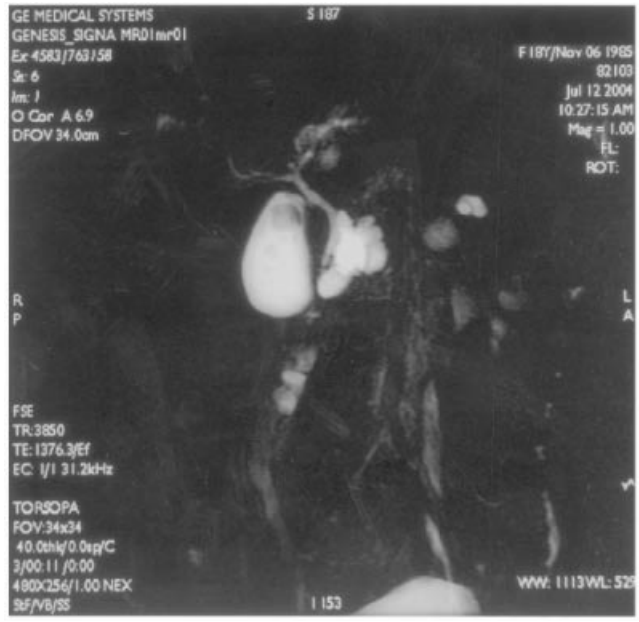

Figure 27.2 ERCP showing dilated bile ducts and gall bladder stone. Courtesy of Dr W.T. Young

Assessment of the severity of acute pancreatitis

In an individual patient, the severity of disease is judged by clinical observation. In an attempt to compare disease

severity between centres, assess the results of therapeutic intervention and perhaps decide referral to specialized centres, various scoring systems have been introduced. One of the earlier scoring systems was introduced by Ranson *et al*.[5] The index takes account of age, white blood cell counts, glucose levels, LDH and AST levels at admission and the decrease in haematocrit, elevation of the blood urea, decrease in serum calcium, pO_2, base deficit and fluid balance at 48 h. Using similar measurements, modified 'Glasgow criteria' were later introduced.[6] These prognostic indices are of proven value in predicting severe disease but suffer from the disadvantage that measurements are made over a period of 48 h. A score of >3 by either system indicates severe disease. The 'APACHE II' can be calculated on admission and is more sensitive and specific at 48 h after admission. The APACHE II grading system has the advantage that it can be measured from admission and throughout the hospital stay.[7] Assessment of disease activity using CT scanning has also been studied and shown good correlation with local complications and mortality.[8]

Management of acute pancreatitis

Mild disease requires only observation and symptom control. Antibiotics are not routinely given. The 20–30% more ill patients need admission to an intensive care unit and careful monitoring. Nutrition is important and there is a debate as to whether the patient should be nourished by enteral routes or by parenteral routes. A meta-analysis suggested that enteral feeding was more appropriate. Compared with parenteral feeding, enteral feeding reduced the number of surgical interventions and the number of infections. Additionally, parenteral feeding is immunosuppressive and favours inflammation.[9] The feeding tube should be placed in the jejunum to prevent pancreatic stimulation.

Routine antibiotic therapy in severe acute pancreatitis is controversial. Although the evidence is slight, a Cochrane review suggested that patients with proven pancreatic necrosis should be given broad-spectrum antibiotics active against gut organisms for up to 2 weeks.[10] In patients with bile duct stones, endoscopic duct clearance, particularly if there are signs of concomitant biliary disease, should be carried out as soon as possible. Patients with gallstones who develop mild acute pancreatitis should undergo cholecystectomy during their index admission. Steroids are the treatment of choice for autoimmune pancreatitis.

Indications for surgery in acute pancreatitis include pancreatic pseudocyst and pancreatic abscess. Removal of necrosed pancreas should be considered in patients with continuing fever after antibiotics who have clear signs on CT scanning. The surgery is hazardous and best done by surgeons skilled in pancreatic surgery. Surgical intervention can be life saving and age alone does not preclude it.

Chronic pancreatitis

Whereas the pancreas is normal before and after an attack of acute pancreatitis, the gland is always histologically abnormal in chronic disease. The histological changes include an increase in the intralobular fibrous tissue, atrophy of the acini and a chronic inflammatory infiltrate. Macroscopically, ductal changes, mainly duct dilatation, occur when there is an obstructive cause of the disease. Pancreatic tissue is difficult to obtain and histological changes are patchy so that the diagnosis of chronic pancreatitis is seldom made histologically.

Incidence and prevalence rates for chronic pancreatitis, particularly in the elderly, are uncertain. Chronic pancreatitis is rarely diagnosed for the first time in patients over 65 years of age. The most common cause of the disease is alcohol, so most cases of chronic pancreatitis present in the fourth and fifth decade of life. Estimated prevalence rates for all ages range from 0.04 to 5%.[11] In an English study of hospital admissions, age-standardized admission rates for chronic pancreatitis rose by 100% in the decade ending in 2000.[12] In the USA, the National Discharge Survey indicated that only 12% of patients were 65 years of age or older.[13]

Causes of chronic pancreatitis

Alcohol is the commonest cause of chronic pancreatitis overall but is less common as a cause in the elderly. In the elderly, autoimmune pancreatitis must be considered; pancreatic insufficiency of unknown origin (possibly vascular insufficiency) occurs most commonly in older persons without other symptoms of pancreatitis. Chronic pancreatitis occurs in chronic ductal obstruction such as that caused by a periampullary tumour, in pancreas divisum in which the head and body of the pancreas develop separately and each has its own duct, in hyperlipoproteinaemia and in hyperparathyroidism. Pancreatic insufficiency is a cause of 'geriatric cachexia'.

Postmortem examinations reveal that pancreatic stones occur in ~15% of patients over the age of 90 years and that changes of chronic pancreatitis are seen. The significance of these findings is uncertain as there is no correlation with clinical disease.[14]

Clinical presentation of chronic pancreatitis

Severe abdominal pain, a characteristic of chronic pancreatitis in younger patients, is less severe or even absent in the elderly. Weight loss, diabetes and fat malabsorption occur.

Occasionally, chronic pancreatitis is recognized when pancreatic calcification is noted on a straight X-ray of the abdomen (Figure 27.3).

Clinical examination is usually normal, although there may be localized tenderness in the epigastrium. Signs of malnutrition occur late in the disease.

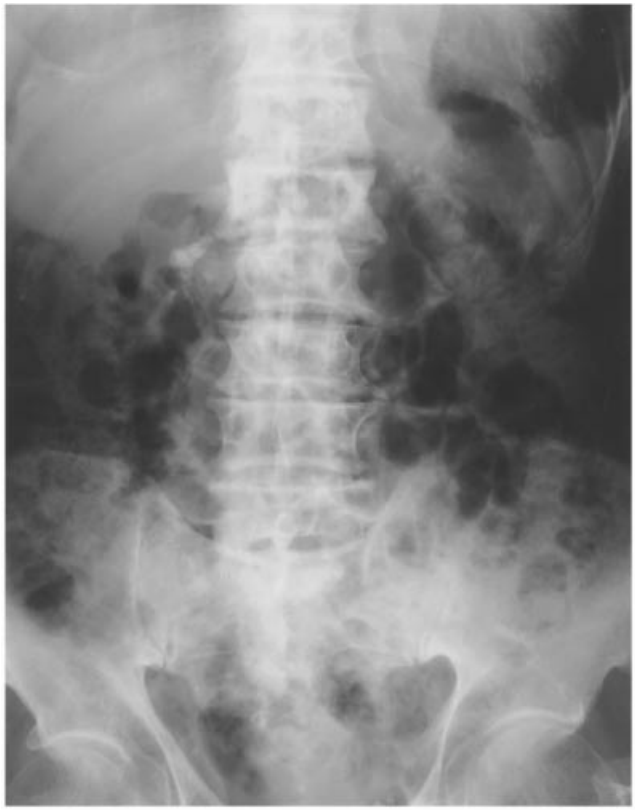

Figure 27.3 Plain abdominal X-ray showing pancreatic calcification in chronic pancreatitis. Courtesy of Dr N. Al-Mohktar

Diagnosis of chronic pancreatitis

Establishing a diagnosis is difficult. Serum amylase and lipase levels are usually normal or only slightly elevated. If there is associated obstruction of the intrapancreatic bile duct, bilirubin and alkaline phosphatase levels are elevated. Steatorrhoea results from exocrine insufficiency and can be recognized by Sudan staining of the stool and quantified when the patient eats a daily diet containing 100 g of fat. Faecal fat excretion resulting from chronic pancreatic disease is usually higher than that seen in other causes of fat malabsorption. Faecal elastase levels fall with ageing and are a sensitive diagnostic test for malabsorption. Measurement of serum vitamin A and β-carotene can be used to screen for fat malabsorption.[15]

Tubeless pancreatic function tests are increasingly valuable in suggesting the diagnosis. The *p*-aminobenzoic acid (PABA) excretion index is based on the ability of pancreatic chymotrypsin to split orally administered *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid. The released PABA is then measured in the urine. The pancrealauryl test is similar. Pancreatic esterases release fluorescein, which is again measured in the urine. Provided that hepatic, renal and intestinal functions are normal, low levels of PABA or fluorescein in the urine suggest pancreatic insufficiency. Analysis of intestinal volume, concentrations of pancreatic enzymes and bicarbonate following a standard test meal or the intravenous administration of cholecystokinin can indicate exocrine insufficiency. The conditions under which the test is performed need to be carefully controlled so its use is confined to those with special experience.

Imaging procedures

Imaging procedures have superseded function studies in the diagnosis of chronic pancreatitis. Plain abdominal radiography may show calcification. Calcification appears more rapidly in patients with alcoholic rather than idiopathic pancreatitis and consequently is less common in the elderly. In about two-thirds of patients, ultrasonography shows swelling of the gland or duct dilatation. CT scanning provides similar information but may be more sensitive.

Endoscopic retrograde pancreatography has become essential in the diagnosis and assessment of chronic pancreatitis. It demonstrates duct abnormalities, which are classified as mild, moderate or severe. Endoscopic pancreatography shows minor abnormalities of the smaller pancreatic ducts, allowing a diagnosis of chronic pancreatitis to be made in patients in whom other imaging procedures have been normal.

Pancreatography is of particular value therapeutically. Duct strictures amenable to dilatation, stenting or partial gland resection may be apparent only endoscopically. Finally, endoscopy is a valuable aid in the diagnosis of pancreatic cancer.

Complications of chronic pancreatitis

Diabetes is more difficult to control in chronic pancreatitis and episodes of hypoglycaemia are likely because of poor diet or malabsorption. Hyperglycaemia is an inevitable consequence of major pancreatic resections (see Chapter 101, Diabetes mellitus). Pancreatic pseudocysts in chronic pancreatitis are less likely to resolve spontaneously than those in acute pancreatitis and often have to be drained. Rupture of a pseudocyst into the peritoneum leads to pancreatic ascites. High amylase levels in the ascitic fluid confirm the diagnosis. Octreotide may help control the ascites by reducing pancreatic secretion. Occasionally, the cyst ruptures into the pleural space, usually on the left side, leading to a pleural effusion. Rarely, a chronic pancreatic pseudocyst may be the source of haemorrhage which can be life threatening. Haemorrhage may also result from oesophageal varices arising from obstruction to the splenic or portal vein by the inflammatory process in the pancreas.[16]

Management of chronic pancreatitis

Pain is less common in the elderly, but when it occurs, it impairs the quality of life. Opiate drugs should be avoided because of the danger of addiction. Non-steroidal anti-inflammatory drugs (NSAIDs) and tricyclic

antidepressants may be useful. The pain is often related to high intraductal pressures and pharmacological attempts to lower the pressures have been made. Cholecystokinin stimulates the release of pancreatic enzymes. Theoretically, increasing intraluminal levels of pancreatic enzymes by orally administered pancreatic enzymes should decrease native cholecystokinin production and lower intraductal pressure, hence relieving pain. The evidence in favour of this approach is slight because of the difficulty in conducting double-blind trials and high placebo response.

Octreotide is a powerful inhibitor of pancreatic secretion and has been used to reduce pancreatic secretion. Its disadvantage is that it has to be given subcutaneously on a daily basis, although long-acting preparations are now available. Its value remains uncertain.

If drug therapy fails to control pain, coeliac axis block is often successful. If endoscopic pancreatography shows duct strictures, stent placement often relieves pain. Surgical pancreatic resection or total pancreatectomy should seldom be considered as a method of pain relief in the elderly.

Attempts to control steatorrhoea by orally administered pancreatic enzymes are useful and the dose should be titrated to achieve maximum effect. Malabsorption of fat-soluble vitamins occurs and should be treated with appropriate supplements.

Pancreatic tumours

Endocrine tumours of the pancreas

Endocrine tumours of the pancreas are rare. Some of the tumours also occur in extrapancreatic sites. The tumours are classified according to the hormone they excrete. The most common tumour is insulinoma, which secretes insulin and gives rise to episodes of hypoglycaemia or even coma. Glucagonoma is associated with weight loss, diabetes and a rash and somatostatinoma gives rise to diabetes, gallstones, weight loss and steatorrhoea. Gastrinoma gives rise to peptic ulcer and weight loss, tumours secreting growth hormone release hormones that give rise to acromegaly, tumours producing ACTH give rise to Cushing's syndrome and tumours producing pancreatic polypeptide result in abdominal pain, gastrointestinal (GI) bleeding and diarrhoea. Most of the tumours have a malignant potential and may be part of the multiple endocrine neoplasia syndrome. Table 27.1 describes the common pancreatic endocrine tumours.[17]

Cystic tumours of the pancreas

These tumours are rare. Serous cystadenomas are small, rarely over 2 cm in size and are of little clinical import. Mucinous cystic neoplasms range from benign to dysplastic to frankly malignant types. Intraductal papillary mucinous tumour was described about 10 years ago and is yet to be studied in detail.[18]

Cancer of the pancreas

Pancreatic cancer is diagnosed in over 7000 people in the UK each year. The diagnosis is difficult to make and only ~15–20% of patients have tumours amenable to surgery at presentation. The 1 year survival rate is around 20% and only 5% of patients are alive 5 years after diagnosis.

The predominant risk factor is old age (Figure 27.4), although there is a relationship to cigarette smoking. Genetic and general medical conditions such as familial breast cancer, hereditary chronic pancreatitis, chronic pancreatitis and diabetes are also risk factors. In many patients, there is a preceding history of depression, often requiring psychiatric help.

Clinical features

Cancer of the head of the pancreas presents with jaundice, often with epigastric or back discomfort. Later in the clinical course, other symptoms of cholestatic jaundice such as itching, pale stools and dark urine occur. Anorexia and weight loss are common. Tumours of the body and tail of the pancreas present more insidiously and are often recognized only when distal spread of the disease has occurred.

Diagnosis of pancreatic cancer

Following initial assessment, ultrasonography is usually the first imaging procedure. The tumour is seldom seen because of overlying gas shadows. If the tumour is in the head of the pancreas, however, bile duct obstruction may occur and the level of the obstruction visualized.

Table 27.1 Pancreatic endocrine tumours

Type	Age at diagnosis (years)	Five year survival rate (%)	Clinical characteristics
Insulinoma	50–60	90	Fatigue, hypoglycaemia
Gastrinoma	60–70	55	Gastric pain, weight loss
Glucagonoma	50–60	90	Weight loss, diabetes, rash
Somatostatinoma	60–70	30	Diabetes, gallstones, weight loss, steatorrhoea
VIPoma	40–60	45	Flushing
Pancreatic peptideomas	40–60	40	None

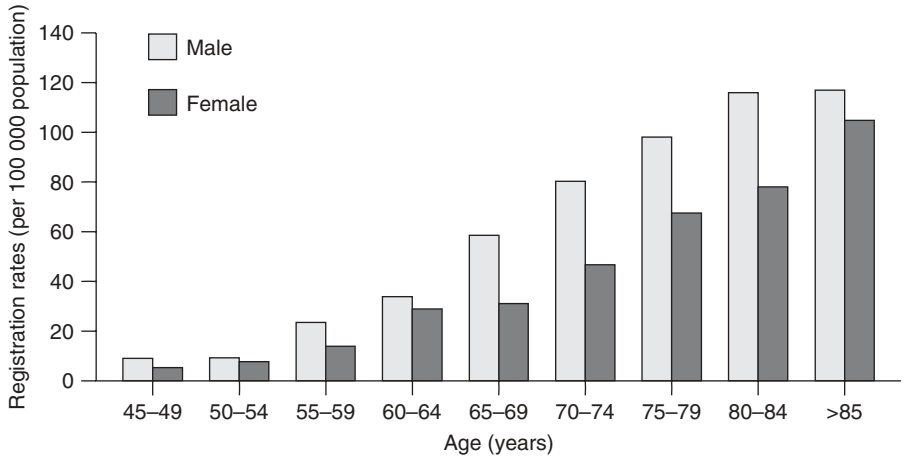

Figure 27.4 Registration rates of pancreatic cancer in Wales. Source: *The Welsh Office Cancer Registration in Wales 1974–1984 and 1984–1988*. HMSO, Cardiff

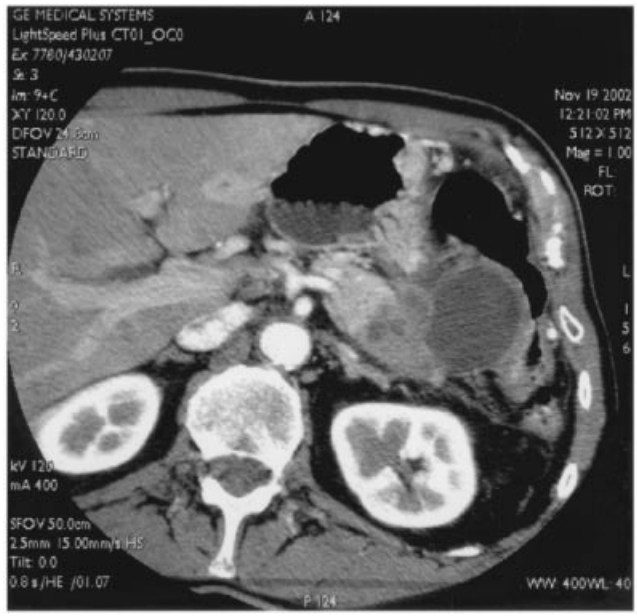

Figure 27.5 Tumour of the pancreatic tail with solid and cystic components. Courtesy of Dr N. Al-Mohktar

CT scanning provides similar information and may help in identifying tumour expansion outside the confines of the gland such as metastatic tumour in the liver or adjacent lymph nodes (Figure 27.5). Endoscopic cholangiopancreatography allows more precise delineation of ductal anatomy and, taken in conjunction with other investigations, helps to decide whether the tumour is resectable. Stent insertion to relieve ductal obstruction at this stage is controversial, should surgery become a management option. A meta-analysis suggested that preoperative biliary drainage was associated with a greater complication rate compared to those patients who underwent surgery alone.[19]

Pancreatic cancer can be confused with chronic pancreatitis. Attempts should be made to verify histologically the diagnosis of a tumour. Tissue or cytological preparations can be obtained by ultrasound or CT-guided fine needle aspiration, although there may be a risk of cancer seeding.

Management of pancreatic cancer

Surgery alone offers the hope of cure and even if performed only offers a 5 year survival rate of 20%. Adjuvant therapy with fluorouracil-based chemoradiation is an option, although others recommend chemotherapy alone.

In patients with unresectable disease, chemoradiation can be used. Gemcitabine is currently under investigation as a radiosensitizer and the agent may also be used as part of a combined chemotherapy protocol.

Palliation is often the only management option. The relief of bile duct obstruction and pain control remain the only treatment modalities that can be offered.

Key points

- Pancreatic cancer is the main pancreatic disease associated with ageing.
- Acute pancreatitis associated with gallstone disease is the commonest cause of acute pancreatitis in the elderly.
- Autoimmune pancreatitis with elevated IgG4 is becoming more commonly recognized.
- There is no good evidence that relates drugs to the development of pancreatitis.
- Although morphological change occurs in the elderly, pancreatic function appears to be maintained.

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SECTION 3

Haematological Disorders

CHAPTER 28

Anaemia

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Introduction

Anaemia has been associated with both frailty[1] and mobility impairment in older persons,[2] and is an independent risk factor for increased mortality over 5 years.[3] Anaemia has been shown to lead to functional impairment,[1,2] and is a risk factor for falls in older persons.[4–6] Anaemia is associated in older adults with decreased muscle density and muscle strength, as measured by ankle extension.[7] Women with a haemoglobin concentration between 130 and 140 g l^{-1} have better mobility and lower mortality compared with those with a haemoglobin concentration of less than 120 g l^{-1}.[2]

Anaemia is strongly associated with an increase in subsequent myocardial infarction and poor outcomes following a myocardial infarction.[8] Among a population-based cohort of older patients with congestive heart failure, anaemia was present in 17% of subjects. Mortality risk was 34% higher in anaemic patients.[9] In a Medicare cohort of patients with congestive heart failure, mortality rate increased by 1.6% for every 1% decrease in haematocrit.[10] Prolonged anaemia also results in left ventricular hypertrophy.[11]

Anaemia is often a comorbid condition complicating other conditions. Subjects who have anaemia tend to be older, have a higher prevalence of a stroke and gastric ulcer, use more medications and have higher creatinine levels. These factors suggest that anaemia may result from underlying disease; however, the association held even when these diseases were excluded.[3]

Quality of life is impaired in persons with anaemia and anaemia produces a high level of fatigue.[12] Vascular dementia, but not Alzheimer's dementia, has been associated with anaemia.[13]

Treatment of anaemia increases haemoglobin concentration, improves quality of life and may decrease mortality.[12,14,15] Patients with congestive heart failure and an ejection fraction of less than 40% who received treatment for anaemia had a 42% improvement in New York Heart Association class score compared with the control patients who had a decrease of 11.4%.[16] Correction of anaemia also produces a decrease in the left ventricular hypertrophy.[11]

Despite the growing evidence of these poor outcomes associated with anaemia in older persons, the diagnosis is often overlooked and, more important, undertreated.[17]

Definition and prevalence

Haemoglobin and haematocrit values differ little between the healthy elderly population and the younger population. Thus, anaemia is not a normal finding in older persons and haemoglobin concentration should not be adjusted downwards in older persons.[18,19] The World Health Organization defines anaemia as a haemoglobin concentration of less than 130 g l^{-1} in men and less than 120 g l^{-1} in women.

The prevalence of anaemia increases with each decade of life over the age of 70 years. In the Established Population data for adults aged 71 years or older, haemoglobin concentration was inversely associated with age. In men and women aged 71–74 years, 9% were anaemic. The proportion of anaemic persons increased differentially with age, reaching 41% for men and 21% for women aged 90 years or older, respectively.[20] A similar trend was reported in the third National Health and Nutrition Examination Survey, where the prevalence jumped from 11% in males aged 70–79 years to 22% in males aged 80–89 years.[21]

There is a marked gender difference in the frequency of anaemia. In a population-based study, the corrected annual incidence of anaemia was higher in men older than 65 years (90.3 per 1000 subjects) compared with women older than 65 years (69.1 per 1000 subjects).[22] This Olmstead County Study showed that before the age of 55 years, the prevalence of anaemia was lower in men (~3%) than women (~6%), but this reversed after age 65 years (prevalence 21% in men and 16% in women). These gender differences in haemoglobin concentration result chiefly from differences in testosterone concentration, and hypogonadism in older males (andropause) is commonly associated with an ~1 g l^{-1} fall in haemoglobin concentration.[23,24] Androgen

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

deficiency may also occur in older women. Furthermore, men who have functional hypogonadism from pituitary adenomas are anaemic,[25] and men with prostate cancer who are undergoing therapy with total androgen blockade are anaemic.[26]

Owing to the increase in prevalence of anaemia with age, the development of anaemia has been often attributed to age alone, called ' idiopathic anaemia of ageing', although ageing in itself cannot directly cause anaemia since studies have shown that in healthy older individuals aged between 60 and 98 years, haemoglobin levels do not change significantly.[19] However, ageing has been shown to be associated with a progressive reduction in haematopoietic reserve, which makes older individuals more susceptible to develop anaemia during haematopoietic stress.[27,28] In addition, reduced bone marrow functional reserve, lower oxygen requirement secondary to lean body mass and reduced erythropoietin production all contribute to causing anaemia in the older population.

A very high prevalence of anaemia occurs in long-term care settings. In 481 long-term care patients with an average age of 81.4 years, the prevalence of anaemia was 31.4%.[2] In another study, the prevalence of anaemia was 40%.[8] In a small study of nursing home residents, of 60 anaemic patients 23% had iron deficiency anaemia, 13% had anaemia of chronic disease, 10% had anaemia of chronic kidney disease, 5% had myledysplastic syndrome and 3% had another form of anaemia. Thus, unexplained anaemia accounted for 45% of all cases and had no diagnostic classification after investigation.[29]

Iron deficiency anaemia occurs in 3% of children aged 1–2 years, 2% of adolescent girls, 1% of adolescent boys and men and 5% of women of childbearing age. In persons older than 50 years, 7% have iron deficiency anaemia.[30] Few data exist on the population prevalence of pernicious anaemia. Data are largely based on surveys of subjects with florid manifestations or from retrospective analyses of previously diagnosed disease. In one population-based survey, the estimated prevalence was 2.7% in women and 1.4% in men. The frequency of pernicious anaemia was higher in both black women (4.3%) and white women (4.0%).[31]

Anaemia associated with chronic renal insufficiency is common. Approximately 13.5 million adults in the USA have a creatinine clearance of 50 ml min^{-1} or less and about 800 000 adults have chronic renal insufficiency-associated anaemia, defined as a haemoglobin concentration of less than 110 g l^{-1}, according to a study of the National Health and Nutrition Examination Survey (NHANES) III data.[22] In that study, a statistically significant decrease in haemoglobin concentration was seen among men starting at a creatinine clearance of 70 ml min^{-1} or less and among women starting at 50 ml min^{-1} or less. At any given level of creatinine clearance, men had a larger decrease in haemoglobin concentration than women. For example, compared to subjects with a creatinine clearance more than 80 ml min^{-1}, the decrease in haemoglobin concentration for subjects with a creatinine clearance of 20 to 30 ml min^{-1} was 10 g l^{-1} in women and 14 g l^{-1} in men.

A substantial number of subjects with chronic renal insufficiency may not have sufficient iron stores to support erythropoiesis. In the National Health and Nutrition Epidemiological Study III, among those persons with a creatinine clearance of 20–30 ml min^{-1}, 46% of women and 19% of men had a transferrin saturation of less than 20% and 47% of women and 44% of men had a serum ferritin of less than 100 ng ml^{-1}.[21]

The most common cause of anaemia in a prevalence study of older persons was anaemia of chronic disease, accounting for 35–40% of cases. Iron deficiency anaemia was responsible for 8–15% of cases. Chronic kidney disease was responsible for 6–8% of cases. Blood loss accounted for 7% and myelodysplasia for about 5%. Vitamin B_{12} deficiency was responsible for another 5%. As in most studies of older persons, a large number of anaemias were undiagnosed despite evaluation.[32]

In the older population, anaemia of chronic disease and anaemia associated with chronic renal disease are the most common causes of anaemia. Renal insufficiency accounts for the greatest percentage of anaemic individuals with the diagnosis of anaemia of chronic disease (27%). Most of these patients have an erythropoietin deficiency. However, other causes of anaemia of chronic disease account for about 73% of cases. These conditions include cancer (non-chemotherapy patients), congestive heart failure, hepatitis C, inflammation, diabetes and rheumatoid arthritis, osteoarthritis, hypertension, stroke, asthma and recent surgery. Often, patients can have more than one cause of anaemia of chronic disease (e.g. iron deficiency, chronic kidney disease and rheumatoid arthritis). For this reason, nutritional anaemias including deficiency in iron, vitamin B_{12} or folate and anaemia due to blood loss and drug side effects should be excluded in persons with chronic disease.

Anaemia of chronic disease is associated with an increase in inflammatory markers such as C-reactive protein (CRP), and due to the common feature of inflammation among the causes of anaemia it has been suggested that anaemia of chronic disease should be referred as anaemia of chronic inflammation (ACI). It is important to differentiate ACI from iron deficiency anaemia as features of both can coexist and overlap. A low serum ferritin is diagnostic of iron deficiency, but in the presence of inflammation ferritin can be normal and therefore iron deficiency cannot be ruled out.[33–35]

Hepcidin, a polypeptide synthesized in the liver and which increases in the presence of chronic inflammation, has been shown to reduce the intestinal absorption of iron

and block the effective use of iron stores from the reticuloendothelial system,[36] suggesting that hepcidin plays a significant role in iron absorption, probably through hormonal action.[37] Anaemia of chronic inflammation may cause a decreased response to erythropoietin.[38] Whether these effects are independent of the inflammatory process or a result of low iron availability is not yet known. Some patients respond to erythropoietin treatment but treatment of anaemia of chronic inflammation is based on treating the underlying inflammatory process.

Differential diagnosis

Manufacture of blood proceeds in the bone marrow in a complex, regulated manner. Anaemia can be due to failure of the bone marrow to manufacture adequate blood components, gradual or rapid blood loss from haemorrhage or a rapid breakdown of blood components (haemolysis) in the marrow or peripherally. Causes of failure of the bone marrow to produce adequate blood components includes primary impairment of haemoglobin synthesis (haemoglobinopathy) or an altered maturation of blood cells (myelodysplastic syndromes) or inadequate nutrients (vitamin B_{12}, folate, pyridoxine or iron) necessary for blood production (see Table 28.1).

A careful differential diagnosis is the cornerstone of management. Several schemes for a differential diagnostic approach have been proposed – none of which is perfect. A corrected reticulocyte count is useful to determine bone marrow function. Anaemia associated with an increased reticulocyte count occurs when the bone marrow responds to red cell destruction (haemolysis) or haemorrhage. The presence of elevated concentrations of unconjugated bilirubin and lactic acid dehydrogenase usually accompanies haemolysis. If these concentrations are normal, haemorrhage from an occult source of blood loss should be sought. A stool occult blood should be obtained, as gastrointestinal bleeding is the most common cause of occult blood loss.

A low or normal corrected reticulocyte count in the presence of anaemia indicates an inadequate bone marrow response. In the presence of a low corrected reticulocyte count, determination of red cell morphology indices is useful (see Figure 28.1).

Table 28.1 Causes of anaemia.

Bone marrow failure:
Genetic (haemoglobinopathy)
Inadequate nutrients (vitamin B_{12}, folate, pyridoxine or iron, trace minerals)
Inadequate erythropoiesis (myelodysplastic syndromes)
Haemorrhage
Haemolysis

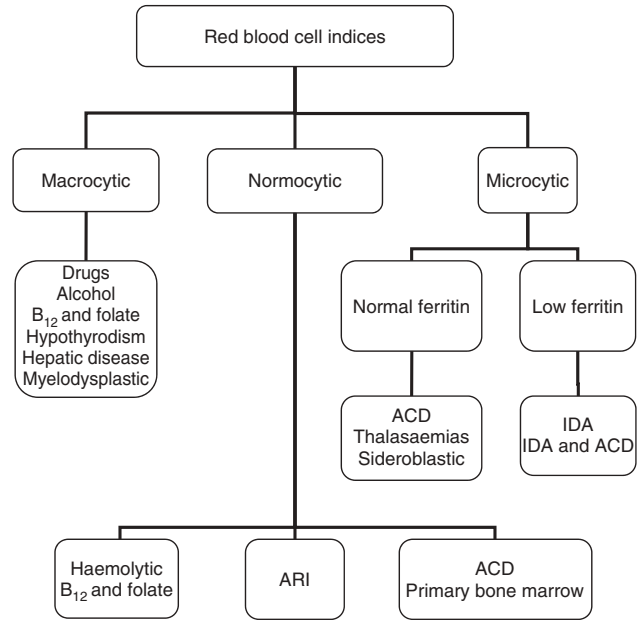

Figure 28.1 Algorithm for diagnosis of anaemia using red blood cell morphology. ACD, anaemia of chronic disease; ARI, anaemia of renal insufficiency; IDA, iron deficiency anaemia. Categories overlap when the morphology of the anaemia may present in one of several ways.

An elevated mean corpuscular volume (macrocytosis) suggests vitamin B_{12} or folate deficiency, hepatic disease, myelodysplasia, hypothyroidism, certain drugs or alcoholism. Measurement of vitamin B_{12} and folate concentrations will determine anaemia due to these causes in the majority of cases. Confirmation of vitamin B_{12} deficiency in those patients who have values in the lower normal range should be obtained, since about 50% of patients with subclinical disease may have normal vitamin B_{12} levels. A more sensitive method of screening for vitamin B_{12} deficiency is the measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B_{12} deficiency. A homocysteine level will be elevated in both vitamin B_{12} and folate deficiencies, but a methylmalonic acid level will be elevated only in vitamin B_{12} deficiency. Renal failure is the only other confounding cause of an elevated methylmalonic acid concentration.

Myelodysplasia syndrome (MDS) can be associated with a normal serum lactic acid dehydrogenase, normal bilirubin and low reticulocyte count. An elevated mean corpuscular volume with abnormalities in red cell corpuscular shape suggests myelodysplastic anaemia when nutritional deficiency, drugs and chemotherapy have been excluded. MDS anaemia is a bone marrow failure state associated with

varying degrees of pancytopenia where at any given time 90% of stem cells are quiescent and 10% are cycling. About half of these patients will have a neutropenia. In MDS, the bone marrow is hypercellular and up to 90% of these cells are undergoing apoptosis at the same time. Cytokines are released which activate caspases, which are cysteine proteases, and these destroy DNA-repairing enzymes. There is an increase in tumour necrosis factor-alpha (TNF-α) in the bone marrow of the majority of MDS patients. Interleukin (IL)−1β may also contribute in the pathogenesis of MDS.[39]

The World Health Organization classification for MDS is shown in Table 28.2.

In subjects with a low or normal mean corpuscular volume, the likely diagnoses include anaemia of chronic disease, anaemia of renal disease and iron deficiency anaemia. Persons with microcytosis, a low serum iron and low ferritin concentrations have iron deficiency anaemia. If the iron is low and the ferritin is high, it is suggestive of anaemia of chronic disease.[40] Thalassaemia syndromes and sideroblastic anaemias (either primary or secondary) may be associated with a microcytic morphology.

Unfortunately, iron deficiency anaemia and anaemia of chronic disease commonly coexist in older persons. In these cases, soluble transferrin receptor may be useful in determining the diagnosis. Circulating soluble transferrin receptors is a relatively new tool in the diagnosis of anaemia. The receptor assay is elevated in iron deficiency anaemia even in the presence of chronic disease, but normal or only slightly raised in anaemia of chronic disease. As ferritin concentrations are elevated in inflammation, liver disease, renal disease, cancer and in some elderly women, soluble transferrin receptors can be of use in making the diagnosis of iron deficiency. Soluble transferrin receptor divided by the logarithm of ferritin concentration (<2.55) is the best method of differentiating anaemia of chronic disease from anaemia of chronic disease associated with iron deficiency anaemia (see Table 28.3).[41] However, there does not appear to be much advantage of these newer, more expensive methods over measuring total iron-binding capacity.[40] A report showed that reticulocyte haemoglobin content (CHr) is sensitive enough to distinguish iron-deficient erythropoiesis even in iron-replete volunteers receiving erythropoietin.[42] An increase in absolute reticulocyte count and CHr begins after oral iron therapy(324 mg by mouth twice per day) for 2 weeks and these two indices increase well in advance of the usual increase of 1 g of haemoglobin after 1 month.

Normocytic morphology is most often associated with anaemia of chronic disease. Anaemia of chronic disease is associated with the presence of renal insufficiency, cancer, congestive heart failure, hepatitis C, inflammation, diabetes, rheumatoid arthritis, osteoarthritis, hypertension, stroke and chronic obstructive lung disease. Also there is an elevation of proinflammatory cytokines such as IL-1, IL-6 and TNF-α. In many older people, IL-6 is chronically elevated and therefore the relationship between anaemia and elevated IL-6 requires further investigation. A recent report suggested that anaemia of chronic disease is associated with a increase in inflammatory cytokines/markers including IL−6.[28,43] In studies of anaemia of chronic disease, renal insufficiency accounts for about 27% of cases. Most of these patients have an erythropoietin deficiency. Figure 28.1 lists

Table 28.2 The WHO classification for MDS.

Refractory anaemia (RA)	Anaemia but white blood cell and platelet counts are normal and bone marrow has <5% blasts
Refractory anaemia with ringed sideroblasts (RARS)	Anaemia similar to those with RA but >15% of the red blood cells as sideroblasts and a normal white blood cell count and platelet count
Refractory cytopenia with multilineage dysplasia (RCMD)	<5% blasts and <15% sideroblasts in the bone marrow and at least two of the blood cell counts are low
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Same as RARS but at least two blood cell counts are low
Refractory anaemia with excess blasts (RAEB)	5–20% blasts in the bone marrow and <5% blast cells in the blood. Often also have a low white blood cell count and platelet count
Myelodysplastic syndrome, unclassified (MDSU)	Pancytopenia but do not show characteristics of other subtypes of MDS
MDS associated with isolated del(5q)	Anaemia and <5% blasts and loss of genetic material from chromosome 5

Adapted from Jaffe ES, Harris NL, Stein H and Vardiman JW (eds). *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*, IARC Press, Lyon, 2001, pp. 47–8.

Table 28.3 Comparison of anaemia of chronic disease and iron deficiency anaemia.

Property	Iron deficiency anaemia	Anaemia of chronic disease
Mean corpuscular volume	Normal or decreased	Decreased or normal
Serum iron	Decreased	Decreased
Total iron-binding capacity	Increased	Normal or decreased
Serum ferritin	Decreased	Increased
Soluble transferritin receptor	Increased	Decreased

the anaemia of renal insufficiency separately, since this anaemia is common and has a distinct therapy.

In chronic kidney disease, there is blunted erythropoietin response, downregulating the response of the erythron to erythropoietin stimulation and probably reducing the survival time of erythrocytes. Hence there is a compensatory increase in erythropoietin levels in an attempt to normalize the haemoglobin concentration. In more advanced stages, this compensation fails, leading to low haemoglobin levels.[44] Anaemia of chronic kidney disease is diagnosed by recognizing renal insufficiency in association with a low erythropoietin level. The Cockcroft–Gault equation is usually used for calculation of estimated creatinine clearance[45] and has been shown to be strongly correlated with more accurate measures of glomerular filtration rate (GFR) measured creatinine clearance.[46]

If the serum creatinine is greater than 2 mg l^{-1}, it is usually unnecessary to measure erythropoietin levels. However, older persons can have a declining GFR in the face of a relatively normal serum creatinine. This results from the loss of lean mass (sarcopenia) associated with ageing or disease-related cachexia, reducing the source of serum creatinine. For example, an 85-year-old woman with a haemoglobin concentration of 100 g l^{-1} who weighs 55 kg and has a serum creatinine of 1.3 mg l^{-1} (normal range) will have a creatinine clearance calculated by the Cockcroft–Gault equation of 27.5 ml min^{-1}. For this reason, a creatinine clearance should be calculated in all older persons with anaemia to determine their renal status. The Cockcroft–Gault equation will demonstrate that the majority of older women with a creatinine of 1.2 mg l^{-1} or greater have severe renal impairment.

Primary bone marrow failure due to drug effects, alcoholism, radiation therapy, chemical exposure and recent trauma or surgery, aplastic syndromes and myelodysplastic syndrome may produce a normocytic morphology. Haemolytic anaemias and, on occasion, nutritional anaemia may present with normocytic morphology and should be excluded.

Haemolytic anaemia

In haemolytic anaemia, increased cell destruction is suggested by an increased lactic acid dehydrogenase, and increased haemoglobin catabolism is suggested by increased levels of indirect bilirubin. Increased clearing of haemoglobin is suggested by decreased levels of haptoglobin, while the bone marrow response is gauged by reticulocytosis. None of these tests are specific or able to distinguish among the various causes of haemolytic anaemia. The causes of a haemolytic anaemia can be classified into disorders of the structure or synthesis of haemoglobin, deficiencies of enzymes that provide the red cell with energy or protect it from chemical damage and disorders of the red cell's membrane.

Defects in haemoglobin structure

Haemoglobinopathies, the inherited diseases of haemoglobin, are very common. Haemoglobinopathies usually result from genetic alterations in the production of haemoglobin; for example, the sickle cell mutation results in a single amino acid substitution in the β-globin chain. Sickle cell disease consists of the homozygous state for the sickle cell gene (HbSS) or a compound heterozygous state for the sickle cell gene combined with either HbC (a β-chain variant) or β-thalassaemia (HbSC disease or sickle cell β-thalassaemia). Heterozygotes have one normal and one affected β-chain gene and produce about 60% HbA and 40% HbS. Homozygotes produce mainly HbS with small amounts of HbF. Compound heterozygotes for HbS and HbC produce almost equal amounts of each variant, whereas those who inherit the sickle cell gene from one parent and β-thalassaemia from the other make predominantly sickle haemoglobin. Sickle cell anaemia should be suspected in any patient with a haemolytic anaemia. It can be confirmed by a sickle cell test, although this does not distinguish between heterozygotes and homozygotes. A definitive diagnosis requires haemoglobin electrophoresis and the demonstration of the sickle cell trait in both parents. The median life expectancy for men and women with homozygous sickle cell anaemia is 42 and 48 years, respectively. In men and women who are heterozygous for HbSC, mean life expectancy is 60 and 68 years, respectively, while a few patients survive into their 70s.[47]

Defects in haemoglobin synthesis

The thalassaemias are classified as α- or β-thalassaemias, depending on which pair of globin chains is synthesized inefficiently. Both β- and δ-chain production are affected in rarer forms of thalassaemias. Patients with the homozygote state for the β-synthesis usually develop severe anaemia in the first year of life. The HbF level is always raised. Severe ineffective erythropoiesis results in erythroid marrow expansion to as much as 30 times the normal level and leads to skeletal changes and hepatosplenomegaly.[48] Transfusion may result in normal growth and development. However, accumulation of iron may lead to damage to the myocardium, pancreas and liver and to infection and folic acid deficiency. Milder forms of β-thalassaemia (thalassaemia intermedia) can be associated with similar bone changes, anaemia, leg ulcers and delayed development in children. Heterozygote β-thalassaemia persons are asymptomatic, with hypochromic microcytic red cells, a low mean corpuscular haemoglobin and low mean cell volume. The HbA2 level is about twice normal. Homozygote persons for α-thalassaemia (Hb Bart's) develop hydrops fetalis syndrome, characterized by the stillbirth of a severely oedematous fetus in the second half of pregnancy. HbH disease is associated with a moderately severe haemolytic anaemia. Carrier states for α-thalassaemia result in a mild hypochromic anaemia with normal HbA2 levels. Other anaemias with an important inherited component include Fanconi's anaemia (hypoplastic anaemia with skeletal deformities), Blackfan–Diamond anaemia (red cell aplasia) and several forms of congenital dyserythropoietic anaemia.

Defects in red cell enzymes

Red cells utilize two main metabolic pathways, either anaerobic metabolism of glucose or reduction of glutathione to protect against injurious oxidants. A large number of inherited enzyme defects have been described. Defects in the pyruvate kinase pathway can cause haemolytic anaemia. Glucose-6-phosphate dehydrogenase deficiency involves a pathway that is critically important to prevent haemolysis.

Precipitated haemoglobin may form a Heinz body, an erythrocyte inclusion that is detected by staining with Crystal Violet. Glucose-6-phosphate dehydrogenase deficiency is gender linked and affects males predominantly. It affects millions of people worldwide, mainly the same groups that are affected by the thalassaemias. Neonatal jaundice, sensitivity to fava beans and haemolytic responses to oxidant drugs are clues to glucose-6-phosphate dehydrogenase deficiency. Several drugs, including Methylene Blue, naphthalene, nitrofurantoin, phenazopyridine, primaquine, sulfonamides and sulfones, Toluidine Blue and trinitrotoluene, have been associated with haemolytic anaemia in persons with glucose-6-phosphate dehydrogenase deficiency.[49]

Defects in the red cell membrane

The red cell membrane is required to maintain the integrity of the cell. There are many inherited defects of the membrane proteins, some of which cause haemolytic anaemia. Hereditary spherocytosis is due to a structural change that makes the cells more leaky and can be treated by splenectomy. Other inherited varieties of elliptical or oval red cells can produce chronic haemolysis and respond to splenectomy.

Accelerated destruction of red cells

The diagnosis of autoimmune haemolysis is based on demonstrating that autoantibodies or complement components are bound to the red cells and are associated with a shortened red cell lifespan. Anaemia results when the rate of red cell destruction exceeds the regenerative capacity of the bone marrow. The direct antiglobulin test was introduced by Coombs *et al*. in 1945 and remains the hallmark in the laboratory diagnosis of autoimmune haemolytic anaemia.[50] The Coombs test demonstrates the presence of immunoglobulins or complement bound to the erythrocyte membrane. The antibodies can be classified into warm, cold and mixed types, depending on the thermal characteristic of the autoantibodies.[51] The diagnosis may be complicated when the haemolysis is associated with another type of anaemia, haemorrhage or blood transfusions or is minor.[52] A large number of conditions have been associated with an autoimmune haemolytic anaemia (see Table 28.4).

Aplastic anaemia

Aplastic anaemia is a failure of the bone marrow. Erythrocytes, granulocytes and platelets decrease to dangerously low levels. The pathophysiology of aplastic anaemia is thought to be immune mediated, with active destruction of blood-forming cells by lymphocytes. The aberrant immune response may be triggered by chemicals and drugs (see Table 28.5), viral infections or by endogenous antigens generated by genetically altered bone marrow cells. Anaemia leads to fatigue, dyspnoea and cardiac symptoms, while thrombocytopenia leads to bruising and mucosal bleeding and neutropenia leads to sharply increased susceptibility to infection.[53]

Aplastic anaemia can be effectively treated by stem cell transplantation or immunosuppressive therapy. Transplantation is curative but is best used for younger patients who have histocompatible sibling donors. Antithymocyte globulin and ciclosporin restore haematopoiesis in approximately two-thirds of patients. However, recovery of blood cell

Table 28.4 Conditions associated with autoimmune haemolytic anaemias.

Warm antibody	Cold antibody
Chronic lymphocytic leukaemia	Primary atypical pneumonia
Hodgkin's disease	Ebstein–Barr virus infection
Non-Hodgkin's lymphomas	Leprosy
Thymomas	
Multiple myeloma	
Waldenstrom's macroglobulinaemia	
Systemic lupus erythematosus	
Scleroderma	
Rheumatoid arthritis	
Infectious disease/childhood viral disorders	
Hypogammaglobulinaemia	
Dysglobulinaemias	
Ulcerative colitis	
Ovarian dermoid cysts	
Immune deficiency syndromes	
Drug-induced (α-methyldopa)	

count is often incomplete, recurrent pancytopenia requires retreatment and some patients develop late complications (especially myelodysplasia).[54]

Paroxysmal nocturnal haemoglobinuria (PNH) is intimately related to aplastic anaemia because many patients with bone marrow failure have an increased population of abnormal cells. These abnormal haematopoietic stem cells lack an entire class of distinctive cell surface proteins, which may convey a selective advantage in resisting immune attack. PNH may be related to aplastic anaemia and myelodysplasia. PNH cells have been identified in 42% of patients with aplastic anaemia and 23% of those with myelodysplasia early in the disease process and before any treatment.[55] Finding a non-immune haemolysis with haemosiderinuria should lead to an investigation for PNH. PNH should be investigated in cases of aplastic anaemia or a venous thrombosis. PNH is a rare disease with the annual incidence of only about four per million persons.[56]

Management

Anaemia due to vitamin B_{12} or folate deficiency is treated by the replacement of the vitamin. Vitamin B_{12} can be replaced either by injections (1000 μg weekly for 1 month, then monthly thereafter), orally (1000 μg daily, which should not be given with food) or intranasally. Folate 1 mg should be used to treat folate deficiency and should be used during the first few weeks of vitamin B_{12} deficiency.

In persons with iron deficiency, the recommended treatment is iron sulfate 325 mg three times per day, providing 195 mg of elemental iron per day.[57–59] The sulfate moiety can cause gastrointestinal distress and, if this occurs, iron in the form of gluconate or fumarate may be helpful. Some experts suggest that iron sulfate once per day may have a similar effect to three times per day dosing if absorption is normal. The duration of iron therapy may be longer when once per day dosing is used. Whatever the chosen dose, a reticulocyte count should be obtained 1 week after starting iron. If there is not a robust reticulocyte response, intravenous iron should be considered. Iron therapy may be discontinued when the ferritin level is normalized (see Table 28.6). Iron should be considered replaced when serum ferritin is maintained above 100 ng ml^{-1}. Once a ceiling ferritin level of 800 ng ml^{-1} has been reached, no more iron should be administered.

Since the introduction of human recombinant erythropoietin in 1989, the treatment of anaemia due to chronic disease has been revolutionized. A linear relationship between GFR and anaemia has been demonstrated. In patients with chronic renal insufficiency, the evaluation of anaemia should begin in women with a haemoglobin concentration of 110 g l^{-1} or less and in men with a haemoglobin concentration of 120 g l^{-1} or less. Anaemia can develop relatively early in the course of a chronic renal failure and has been associated with a serum creatinine as low as 2.0 mg l^{-1}.[60]

Significant anaemia has been noted when the calculated GFR is less than 20–35 ml min^{-1}.[61,62] In patients with an impaired renal function and a normochromic, normocytic anaemia, it is rare for the serum erythropoietin level to be elevated. Therefore, measurement of erythropoietin levels in such patients is not likely to guide clinical decision-making or therapy. While the majority of persons on dialysis receive erythropoietin, there are many persons who have chronic renal insufficiency who do not receive erythropoietin. This is particularly true among older persons.

As may be expected with increased blood volume, erythropoietin therapy increases blood pressure, necessitating close monitoring in patients with known cardiovascular disease. The haemoglobin level should not exceed 120 g l^{-1} in correcting anaemia in renal insufficiency.

Erythropoietin has been shown to increase the haemoglobin concentration in patients with anaemia associated with surgical blood loss, cancer, chemotherapy, anaemia associated with drug therapy for AIDS or hepatitis C virus, myelodysplastic disease and the anaemia of chronic disease, especially when associated with rheumatoid arthritis. Several conditions may result in an inadequate response to erythropoietin therapy, including coexisting iron, vitamin B_{12} or folate deficiency, acute or chronic infections, inflammatory diseases, chronic blood loss, haemoglobinopathies, multiple myeloma, malnutrition, haemolysis, malignancy, hyperparathyroidism and hypogonadism. Failure to respond to erythropoietin should trigger an evaluation for these conditions (see Table 28.7).

Table 28.5 Drugs associated with aplastic anaemia.

Group 1: marrow aplasia expected	Group 2: marrow aplasia idiosyncratic
Antineoplastic drugs	Antiarthritics (gold salts, D-penicillamine, colchicine)
Alkylating agents (busulfan, cyclophosphamide, melphalan, nitrogen mustard)	Antibiotics (sulfonamides)
Antimetabolites (fluorouracil, mercaptopurine, methotrexate)	Anticonvulsants (carbamazepine, hydantoins, felbamate)
Cytotoxic antibiotics (daunorubicin, doxorubicin, mitoxantrone)	Antidysrhythmics (quinidine, tocainamide)
Benzene	Antihypertensives (nifedipine)
Benzene-containing chemicals	Antiplatelets (clopidogrel, ticlodipine)
Kerosene	Antithyroids (carbimazole, methimazole, propylthiouracil)
Carbon tetrachloride	Diuretics (acetazolamide, chlorothiazide, furosemide)
Stoddard's solvent	Non-steroidal anti-inflammatory drugs (butazones, indomethacin, ibuprofen)
Toluene	Hypoglycaemics (chlorpropamide, tolbutamide) Psychotropics (chlordiazepoxide, chlorpromazine, other phenothiazines)

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Table 28.6 Approach to the management of anaemia.

Diagnosis	Treatment
Iron deficiency	Ferrous sulfate 325 mg 1–3 times daily
Vitamin B_{12} deficiency	Vitamin B_{12} 1000 μg orally or intramuscularly
Folate deficiency	Folate 1 mg daily
Anaemia of chronic kidney disease	Epoetin alfa 10 000 U weekly or darbepoetin alfa 60 μg every 2 weeks to target haemoglobin 100–120 g l^{-1}
Anaemia of chronic disease	Treat underlying condition; consider epoetin alfa weekly or darbepoetin alfa every 2 weeks to target haemoglobin 100–120 g l^{-1}

Table 28.7 Potential causes for inadequate response to erythropoietin therapy.

Iron/vitamin B_{12}/folate deficiency
Infection/inflammation (e.g. access infections, surgical inflammation, AIDS, systemic lupus erythematosus)
Chronic blood loss
Osteitis fibrosa
Haemoglobinopathies (e.g. α- and β-thalassaemias, sickle-cell anaemia)
Multiple myeloma
Malnutrition
Haemolysis
Aluminium toxicity
Malignancy
Hyperparathyroidism
Hypogonadism
Other: angiotensin-converting enzyme inhibitors (reported, but not verified)

The target haemoglobin for optimum outcomes with erythropoietin therapy has been the focus of several trials. The Normal Haemoglobin Trial[63] found a 30% increase in death and non-fatal myocardial infarction in patients who had clinical evidence of heart failure and who were receiving dialysis and who received erythropoietin to maintain a haematocrit of 42% versus a similar group who maintained a haematocrit of 30%.

The Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial evaluated patients with chronic kidney disease for a mean duration of 16 months.[64] Patients had a mean haemoglobin level of 101 g l^{-1} and a mean GFR of 27 ml min^{-1} and about 50% were diabetic at baseline. Patients were randomly assigned to receive a dose of epoetin alfa targeted to achieve a haemoglobin level of 135 g l^{-1} or to receive a dose targeted to achieve a haemoglobin level of 113 g l^{-1}. The primary endpoint was a composite of death, myocardial infarction, hospitalization for congestive heart failure and stroke. The use of a target haemoglobin level of 13.5 g dl^{-1} (as compared with 11.3 g dl^{-1}) was associated with increased composite risk and no incremental improvement in the quality of life.

In the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial, patients with stage 3–4 chronic kidney disease and mild to moderate anaemia (haemoglobin 110–125 g l^{-1}) were randomized to treatment with epoetin beta to a target haemoglobin range of either 130–150 or 105–115 g l^{-1}.[65] The primary outcome was a composite of eight cardiovascular events. After following these patients for 3 years, the investigators found that there was no significant difference in cardiovascular event rates or in all-cause mortality between the two groups, but an increase in blood pressure was noted in the normalization group.

The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)[66] randomized subjects with diabetes,

chronic kidney disease and moderate anaemia who were not undergoing dialysis to darbepoetin alfa to achieve a haemoglobin level of 130 g l^{-1} or to placebo with rescue darbepoetin alfa if the haemoglobin level was less than 90 g l^{-1}. The primary endpoint of the study was a composite outcome of death or a cardiovascular event (non-fatal myocardial infarction, congestive heart failure, stroke or hospitalization for myocardial ischaemia) and of death or end-stage renal disease. This study showed that the normalization of the haemoglobin by use of darbepoetin alfa did not reduce the risk of either death or a cardiovascular event or death or a renal event and was associated with a higher risk of stroke.

A meta-analysis of the 27 trials selected demonstrates that a higher haemoglobin target is associated with increased risks for stroke [relative risk (RR) 1.51], hypertension (RR 1.67) and vascular access thrombosis (RR 1.33) compared with a lower haemoglobin target. No statistically significant differences in the risks for mortality (RR 1.09), serious cardiovascular events (RR 1.15) or end-stage kidney disease (RR 1.08) were observed, although point estimates favoured a lower haemoglobin target.[67]

Blood transfusions are often given to older persons who become symptomatic, drop their haemoglobin concentration below 80 g l^{-1} or who have an acute bleed. However, despite adequate careful cross-matching of blood, complications are common. Transfusion reactions can lead to haemolysis and fever. Transfusions are often associated with circulatory overload in older persons.

Since the original description of blood-borne hepatitis A, numerous infections including AIDS have been transmitted to patients during blood transfusions. For these reasons, attempting to maintain haemoglobin concentration by other approaches is very important in the long-term care resident. Human recombinant erythropoietin administration can reduce blood transfusion requirements.[22]

Erythropoietin stimulates bone marrow and reduces transfusion requirements during chemotherapy or radiotherapy. However, data from a meta-analysis of 53 trials in cancer patients receiving erythropoietin during active chemotherapy treatment found increased mortality during the active study period (combined hazard ratio 1.17) and a slight increase in overall mortality during the active study period and a slight decrease in subsequent overall survival.[68] Because of the findings, a black box warning was added to erythropoiesis-stimulating agent labels in 2008 stating that these agents shorten survival and increase risk for cancer progression in patients with breast, non-small-cell lung, head and neck, lymphoma and cervical cancers. Prescription of erythropoiesis-stimulating agents is limited in patients with cancer. Guidelines for the use of erythropoiesis-stimulating agents in patients with cancer are shown in Table 28.8 and are available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm.

Table 28.8 Guidelines for use of erythropoiesis-stimulating agents in patients with cancer.

1. Erythropoiesis-stimulating agents (ESAs) are indicated for the treatment of anaemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for red blood cell transfusions in patients with metastatic, non-myeloid malignancies
2. ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure
3. Use ESAs only for treatment of anaemia due to concomitant myelosuppressive chemotherapy
4. ESA therapy should not be initiated at haemoglobin levels $\geq$10 g dl^{-1} and dosing should be adjusted to maintain the lowest haemoglobin level sufficient to avoid red blood cell transfusion
5. Discontinue ESAs following the completion of a chemotherapy course
6. ESAs have not been demonstrated in controlled clinical trials to improve symptoms of anaemia, quality of life, fatigue or patient wellbeing
7. ESAs are not indicated for use in patients receiving hormonal agents, therapeutic biological products or radiotherapy unless receiving concomitant myelosuppressive chemotherapy

Source: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm.

Conclusion

The positive clinical outcomes for treating anaemia, such as reduction in transfusion requirement, suggest that a haemoglobin concentration of less than 120 g l^{-1} should be investigated and treated whenever possible. The differential diagnosis of anaemia is complex, including inherited or acquired anaemias that persist into older age. Chronic kidney disease and its associated anaemia are very likely underdiagnosed in older persons. Erythropoietin should clearly be considered in all anaemic older adults with chronic kidney disease whose serum creatinine is greater than 2 mg l^{-1}. A calculated creatinine clearance should be done to identify patients with chronic renal failure whose creatinine may be less than 2 mg l^{-1}. The availability of recombinant erythropoietin and newer products with a longer half-life make the goal of correcting anaemia and improving patient outcomes a priority.

Key points

- Anaemia has been associated with frailty, functional impairment, falls and increased mortality.

- Positive clinical outcomes for treating anaemia demand investigation and treatment whenever possible.
- The differential diagnosis of anaemia is complex.
- Anaemia associated with chronic kidney disease remains underdiagnosed in older persons.
- Newer treatment modalities facilitate the goal of correcting anaemia and improving patient outcomes.

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CHAPTER 29

Disorders of haemostasis

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Introduction

Bleeding causes or contributes to the death of about 5% of the elderly population. This is primarily due to intracranial and subarachnoid haemorrhage, ruptured aortic aneurysm and gastrointestinal bleeding from peptic ulcer and gastric or colonic malignancy. Bleeding due to primary disorders of haemostasis in the elderly is relatively rare. Severe congenital bleeding diatheses are usually diagnosed at a young age, with the majority of them now being treatable and carrying a normal life expectancy, while acquired disorders of haemostasis are an uncommon cause of death except as part of the syndrome of multiorgan failure. Most bleeding in the elderly is localized and the result of a specific underlying pathology, frequently malignancy. Bleeding disorders can be classified as being due to abnormalities of platelet number or function, disorders of the coagulation cascade and disturbances of the vascular endothelium and connective tissues.

Thrombotic disorders are far more significant causes of morbidity and mortality in the elderly age group. Arterial thrombosis and atheroma cause cardiovascular disease, cerebrovascular disease and peripheral vascular disease. Likewise, venous thromboembolism is primarily a disease of older age and is now recognized as being due to a combination of both circumstantial and underlying genetic factors. Ageing itself does not result in either any major or significant changes in the range of the common coagulation tests, such as the activated partial thromboplastin time (APTT), prothrombin time (PT) or thrombin time (TT), or in the level of fibrinogen or other specific coagulation factors and inhibitors. Likewise, the platelet count does not alter with age. There is, however, convincing evidence from sensitive markers of coagulation activation that background turnover of the proteins is increased with age.[1] Although there are no major changes in haemostasis that occur with increasing age, diseases that may result in bleeding problems or thrombosis are more common and their consequences more serious in the elderly (Table 29.1).

Disorders of platelet number

The normal platelet count is between 140 and 400 $\times 10^9\,l^{-1}$. There is, however, some reserve and haemostasis is normal with a platelet count of above 80 $\times 10^9\,l^{-1}$, assuming normal platelet function. If the platelet count falls below this value, the bleeding time progressively prolongs but spontaneous haemorrhage, in particular intracerebral haemorrhage, does not occur until the platelet count falls below 20 $\times 10^9\,l^{-1}$. Platelet numbers can be decreased by three mechanisms: decreased production in the bone marrow, increased peripheral destruction, immune consumption and splenic pooling in gross splenomegaly with hypersplenism. In addition, adverse effects of drugs should always be considered as a possible cause in any case of thrombocytopenia.[2]

Decreased platelet production

Decreased platelet production can be due to any condition that causes infiltration and replacement or aplasia of the bone marrow, for example, aplastic anaemia, leukaemia, lymphoma, carcinoma and myelodysplasia or deficiency of vitamin B_{12} and folate in megaloblastic anaemia.

Increased peripheral destruction

In childhood, immune thrombocytopenic purpura (ITP) is usually an acute self-limiting condition, frequently precipitated by a viral infection, which spontaneously remits. In adults, ITP often has an insidious onset without an obvious precipitant cause and runs a chronic course over many months and years, occasionally being extremely refractory to treatment. ITP is due to the production of an autoantibody against platelets, usually directed against the platelet membrane-specific glycoproteins. The binding of the antibody to the platelet surface antigen results in the uptake of the platelet–antibody complex by the reticuloendothelial system and premature destruction of

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 29.1 Coagulation tests.

Test[a]	Test of	Causes of abnormality
APTT/KCCT	Intrinsic and common pathways	Factor VIII, IX, XI, XII, II, V or X deficiency, or inhibitor Lupus anticoagulant Heparin
PT	Extrinsic and common pathways	Factor VIII, II, V or X deficiency, or inhibitor Liver disease Warfarin
TT	Fibrinogen polymerization	A-hypo-dysfibrinogenaemia Heparin Raised FDP
Fibrinogen	Fibrinogen quantity	A-hypo-dysfibrinogenaemia
FDP/D-dimer	Fibrinolysis	Disseminated intravascular coagulation Venous thrombosis
Platelet count	Platelet number	Thrombocytopenia or thrombocytosis
Bleeding time	*In vitro* platelet function	Thrombocytopenia Functional platelet defect
PFA	*In vitro* platelet function	Aspirin

[a]FDP, fibrin Degradation Products; KCCT, kaolin cephalin clotting time.

the platelet. Destruction occurs primarily in the spleen and also in the liver and bone marrow and platelet survival is decreased from the normal 7–10 days to only a few hours. Diagnosis is based on the finding of true thrombocytopenia, together with a normal bone marrow showing normal or increased numbers of megakaryocytes, the progenitor cells of platelets and an absence of an alternative cause of excessive peripheral platelet destruction. A low platelet count from an automated blood cell analyser should always be repeated and the blood film should be examined to exclude artefactual thrombocytopenia due either to the sample having clotted or to platelet clumping caused by the anticoagulant. The clotting screen should be normal. ITP in adults, unlike in childhood, seldom remits spontaneously. The initial treatment is with prednisolone, $1\,mg\,kg^{-1}$ daily or intravenous immunoglobulin $0.4\,g\,kg^{-1}$ daily for 5 days. The condition is usually steroid responsive but frequently steroid dependent, and attempts to withdraw the steroids result in recurrence of thrombocytopenia. Often, the platelet count will stabilize at an acceptable level of above $50 \times 10^9\,l^{-1}$ on no steroids or only a minimal dose, and in the absence of symptoms this is often well tolerated for many years. If there is no response to steroids or an unacceptably high dose is required to maintain a satisfactory platelet count, alternative therapies include intravenous immunoglobulin, $400\,mg\,kg^{-1}$ per day for 3–5 days, which usually raises the platelet count for around 3 weeks and sometimes results in a sustained remission and splenectomy, which, although it does not prevent autoantibody production, does prevent premature platelet destruction by the spleen. A splenectomy is successful in achieving complete remission in about 50–75% of cases progressing as far as surgery. Splenectomy should not, however, be undertaken lightly as it is not without hazard, particularly in the thrombocytopenic patient. In addition to the operative risks, there is the risk of subsequent overwhelming postsplenectomy sepsis: preoperative pneumococcal *Haemophilus influenzae*, a meningococcal vaccination and postoperative penicillin prophylaxis should therefore be given. For those in whom a splenectomy is contraindicated or fails, immunosuppressive therapy with azathioprine or cyclophosphamide is sometimes effective. Danazol, vitamin C, interferon and ciclosporin have all been tried with varying efficacy, as has extracorporeal absorption of the antibody with a protein A column. New thrombopoietin agonists are becoming available which may have a role in the management of severe symptomatic or refractory ITP. In difficult and refractory cases, none of these therapies is frequently or consistently successful.[3]

Increased pooling of platelets

Under normal circumstances, 25% of the peripheral platelet pool is sequestered within the spleen at any one time. With increasing and massive splenomegaly, this can increase to more than 90%, resulting in a peripheral platelet count falling even to $50 \times 10^9\,l^{-1}$. Bleeding, however, is rare as the platelets appear to be mobilized during haemostatic challenge and the platelet mass is usually normal.[4]

Thrombocytopenia due to drugs

Drugs can cause thrombocytopenia by direct bone marrow suppression, for example, cytotoxic drugs, alcohol and chloramphenicol or by inducing an immune response – those most commonly being implicated are aspirin, paracetamol, antibiotics, anticonvulsants, diuretics and other miscellaneous drugs such as tolbutamide, quinine and quinidine. Heparin causes a characteristic syndrome of heparin-induced thrombocytopenia (HIT), which, unlike other drug-induced causes of thrombocytopenia, is associated not only with decreased platelet survival and thrombocytopenia but also with platelet activation and hence arterial and venous thrombosis.

Consequently, this condition is associated with severe morbidity, due to severe venous or arterial thrombosis and a mortality of around 30%. It is more common with unfractionated heparin than with low molecular weight heparin,

but can occur with either. Patients receiving heparin for both prophylactic and therapeutic indications should have their platelet counts regularly monitored to anticipate this serious complication. Treatment of suspected HIT involves immediate withdrawal of heparin and commencement of an alternative method of anticoagulation, such as hirudin or heparan but not warfarin.[5]

Functional platelet defects

By far the most common platelet functional defect (Table 29.2) is that acquired following treatment with aspirin. Aspirin works by irreversibly acetylating the platelet enzyme prostaglandin synthase and thereby decreases platelet reactivity and aggregation for the platelet's entire lifespan. Aspirin prolongs the skin bleeding time. In recent years, aspirin has become established in the treatment of acute arterial thrombotic events, such as unstable angina and myocardial infarction, and in the secondary prophylaxis of myocardial infarction and transient ischaemic attack and stroke. There is a trend towards decreasing the dose of aspirin, which not only decreases gastrointestinal toxicity but also results in the platelet being irreversibly acetylated by aspirin in the portal circulation; with low total dose, aspirin is then deacetylated within the liver, resulting in no systemic bioavailability of aspirin and thus in no inhibition of the beneficial effects of endothelial cell prostacyclin production. Clopidogrel is another orally active anti-platelet agent which acts by irreversible inhibition of the platelet ADP receptor. Other drugs that affect platelet function include non-steroidal anti-inflammatory drugs (NSAIDs), high doses of penicillin and cephalosporins and some antidepressants and anaesthetics. Abnormal platelet function can occur in any of the myeloproliferative disorders, namely primary proliferative polycythaemia, essential thrombocythaemia, chronic myeloid leukaemia and myelofibrosis, leading to both bleeding and thrombosis. Bleeding is paradoxically more common with raised platelet counts, especially when greater than $1000 \times 10^9\ l^{-1}$.

Similarly, in myelodysplastic syndromes, in addition to the frequent thrombocytopenia, abnormal platelet function is common and bleeding can cause severe morbidity, requiring platelet transfusion; bleeding and infection are the most common causes of death. Abnormalities of platelet function leading to a prolonged bleeding time frequently occur in uraemia. This improves with dialysis and can be specifically treated, if necessary, with both cryoprecipitate and desmopressin (DDAVP). An acquired platelet function defect, due primarily to proteolytic degradation of platelet surface glycoproteins by plasma, occurs during extracorporeal circulation in cardiopulmonary bypass. It can be ameliorated by the use of the fibrinolytic inhibitor aprotinin, but may on occasion require platelet transfusion in addition. Congenital functional platelet defects are extremely rare, with an incidence of less than one per million of the population. Deficiency of the platelet-specific glycoprotein Ib, which allows interaction with the von Willebrand factor, occurs in Bernard–Soulier syndrome and deficiency of the platelet surface glycoprotein IIb/IIIa occurs in Glanzmann's thrombasthenia. Deficiency of platelet alpha and dense granules, which are usually released upon platelet aggregation and are involved in recruitment of large numbers of platelets into the platelet plug, are deficient in storage pool disease.[6]

Table 29.2 Causes of acquired platelet functional defects due to drugs, especially aspirin.

Myeloproliferative syndromes
Myelodysplasia
Uraemia
Cardiopulmonary bypass

Hereditary coagulation defects

Severe deficiency (<0.01 IU ml^{-1}) of factor VIII (haemophilia A) or factor IX (haemophilia B) will have been diagnosed at a young age and management of these conditions is highly specialized and age independent. Spontaneous bleeding into muscles and joints is frequent and is managed by infusions of appropriate clotting factor concentrates (Figure 29.1). In addition, many of the older patients have severe complications of advanced haemophiliac arthropathy and often hepatic impairment due to chronic infection with hepatitis viruses, especially hepatitis C virus. Haemophilia A and B both have gender-linked inheritance and occur in males. Mild (>0.05 IU ml^{-1}) and moderate ($0.01–0.05$ IU ml^{-1}) cases may have escaped diagnosis until a later age and will not present until they have a severe haemostatic challenge such as surgery, which can occur at any age. These patients will have a long APTT and specific factor assays will reveal the diagnosis. They can usually be managed with desmopressin, a long-acting synthetic analogue of vasopressin, the antidiuretic hormone, rather than with clotting factor concentrates, with the attendant savings on cost and reduced risk of viral transmission. Female carriers of haemophilia A and B usually have around half the normal levels of the respective clotting factor, although, owing to the randomness of the lyonization effect (random inactivation of one X chromosome in all female cells), up to 30% of carriers will have factor VIII or factor IX levels sufficiently low to require treatment at times of surgery; conversely, many carriers have entirely normal levels of factor VIII and factor IX, and, therefore, carrier status cannot be determined accurately simply by measuring

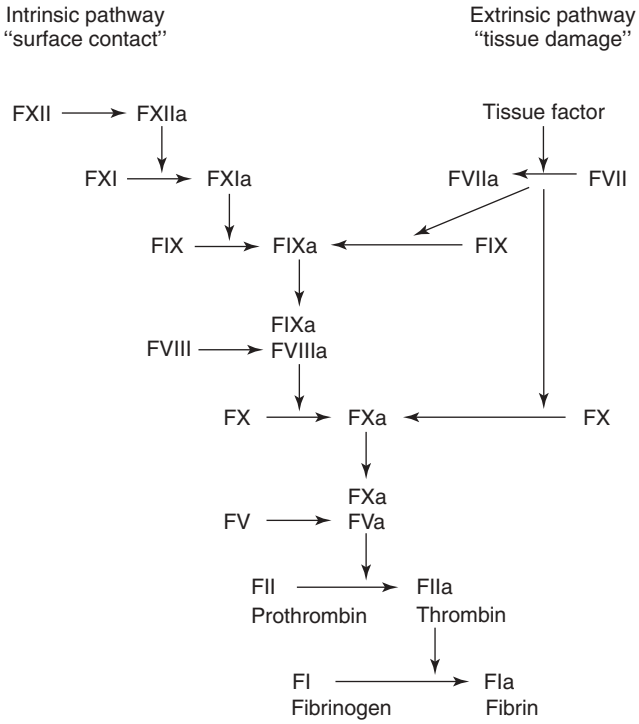

Figure 29.1 Coagulation cascade.

the appropriate factor levels but instead requires genetic analysis.

Von Willebrand's disease is extremely common and has an incidence of up to 1% in the general population. It is autosomally dominantly inherited and, therefore, occurs in males and females equally. The majority of cases are mild; the condition is significantly underdiagnosed and in milder cases bleeding occurs only with significant haemostatic challenges. Consequently, mild von Willebrand's disease can present and be diagnosed at any age. Von Willebrand's disease is due to a decreased concentration of the protein von Willebrand factor, which is important in mediating platelet adhesion to the subendothelium; von Willebrand factor also circulates non-covalently bound to coagulation factor VIII and so protects factor VIII from premature proteolytic degradation. Therefore, in von Willebrand's disease, diminished levels of the von Willebrand factor result in both a mild platelet defect and a mild defect of the coagulation cascade consequent upon the diminished amounts of factor VIII. Unlike in haemophilia, the skin bleeding time is increased and bleeding tends to be primarily mucocutaneous, with epistaxis, gum bleeding, gastrointestinal bleeding and menorrhagia. Diagnosis and classification require the determination of factor VIII concentration, the von Willebrand factor antigen and the von Willebrand factor activity, by use of the ristocetin cofactor activity or collagen binding activity and analysis of the von Willebrand factor multimer distribution. Mild type I cases can usually be treated with desmopressin prior to significant haemostatic challenge, whereas the rarer, more severe forms of von Willebrand's disease usually require treatment with clotting factor concentrates, which should contain both factor VIII and the von Willebrand factor.[7]

Acquired coagulation defects

Probably the most commonly acquired coagulation defect (Table 29.3) in the elderly is iatrogenic, because of the use of the anticoagulants heparin and warfarin. Heparin is given parenterally and acts by potentiating the action of antithrombin to inhibit thrombin. It is a difficult drug to use, with a narrow therapeutic range, complicated pharmacokinetics and significant interpatient variation in dose requirements. Insufficient heparin will result in thrombosis or extension of previously existing thrombosis, while excess treatment rapidly precipitates haemorrhage, which is potentially life threatening. Heparin infusion should be monitored by use of the APTT; the therapeutic range is a ratio of between 1.5 and 2.[8] All the active drugs are now being used for thromboprophylaxis and will shortly be used for the treatment of venous thromboembolism. Dabigatran is an orally active direct thrombin inhibitor and rivaroxaban is an orally active direct factor Xa inhibitor for use in prophylaxis of high-risk surgery and is already proven to be beneficial and it is likely they will be used in the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and replace warfarin for the majority of cases of patients in atrial fibrillation. There are no data yet as to whether they can be used in patients with recurrent thrombosis or thrombophilia or patients with prosthetic heart valves. The introduction of low molecular weight heparins for both prophylaxis and treatment of venous thrombosis has the significant advantages of a longer half-life, increased bioavailability and more predictable pharmacokinetics, and consequently they can be given by once-daily subcutaneous injection without the need for monitoring, even in the doses required for treatment. Since low molecular weight heparin has a greater effect on factor Xa than on thrombin (IIa), it cannot be monitored with the APTT but instead requires an antifactor Xa

Table 29.3 Causes of acquired coagulation defects.

Heparin
Warfarin
Liver disease
Specific coagulation factor inhibitors
Disseminated intravascular coagulation
Paraproteins

assay. However, in overdosage, even low-molecular weight heparin will prolong the APTT and bleeding under these circumstances may require neutralization of the heparin with protamine sulfate.[9]

Warfarin, likewise, is a drug with a narrow therapeutic range, complicated pharmacokinetics and multiple drug interactions, and significant haemorrhagic consequences if given in overdose. Warfarin also requires careful monitoring. There are well-established guidelines for the treatment of venous thrombosis, these being an international normalized ratio (INR) of 2–3 for uncomplicated thrombosis and 3–4 for recurrent and complicated thrombosis or in patients with the presence of artificial prosthetic heart valves or similar.

Liver disease is a common cause of an acquired coagulation disorder. In addition to being the site of synthesis of the majority of coagulation proteins, the liver is also extremely important in the clearance of activated clotting factors. In addition, liver disease is often also associated with dysfibrinogenaemia, due to increased deposition of sialic acid residues on fibrinogen resulting in charge repulsion and failure to polymerize, and hypofibrinogenaemia, due to failure of synthesis. Furthermore, liver disease often causes portal hypertension and hypersplenism with consequent thrombocytopenia due to splenic pooling of platelets. The coagulation defect in liver disease first manifests as a prolongation of the PT and initially is due to decreased production of the active forms of the vitamin K-dependent clotting proteins, factors II, VII, IX and X. Consequently, vitamin K may be of some use in correcting the coagulation defect in early liver disease. Vitamin K takes a minimum of 6 h to work and its effect is maximal at 24 h. In more advanced liver disease, there is a decreased production of all clotting factors and fibrinogen, except for factor VIII, and vitamin K is usually not effective.[10] Disseminated intravascular coagulation is caused by a wide variety of triggering factors and mechanisms and is discussed elsewhere.

Thrombotic thrombocytopenic purpura presents as a classic pentad of fever, thrombocytopenia, neurological and renal involvement and a microangiopathic haemolytic anaemia with red cell fragmentation. It has recently become clear that the majority of cases of TTP are due to an autoimmune deficiency of ADAMST13, an enzyme present in the plasma, that cleaves high molecular weight von Willebrand factor multimers. These ultra-high von Willebrand factor multimers are released from endothelial cells and are usually processed by ADAMST13. If ADAMST13 is deficient, these ultra-high von Willebrand factor multimers are able to cause spontaneous aggregation of platelets to the endothelial cells causing microvascular thrombosis and hence the symptoms of TTP. High-volume plasma exchange results in removal of the antibody and the ultra-high molecular weight multimers, while replacement with plasma results in the patient receiving active enzyme and normal von Willebrand factor multimers. The autoimmune component can be treated either with prednisolone or, more recently, infusions of rituximab. The coagulation tests, however, usually remain normal or only very mildly deranged, in contradistinction to the case in disseminated intravascular coagulation, where thrombocytopenia is accompanied by profound disturbances of coagulation. The treatment is with aggressive, large-volume plasma exchange and plasma transfusion and will involve liaison with haematologists and renal physicians.[11]

Acquired factor VIII inhibitors are rare but their incidence is increasing as the population ages. They can occur spontaneously or in association with an underlying autoimmune or lymphoproliferative disorder. Their management involves both treatment of the active bleeding episode and subsequent efforts to remove or neutralize the antibody. The latter usually involves immunosuppression, although occasionally acquired inhibitors will resolve spontaneously. Treatment of bleeding episodes may require high doses of factor VIII and the use of activated prothrombin complex concentrates or recombinant factor VIIa. Data from the United Kingdom Haemophilia Centre Doctors Organisation has recently shown that the mortality from acquired haemophilia is surprisingly low and that in the elderly patient group sepsis, an effect of immunosuppression, actually causes more death than bleeding.

Paraproteinaemias can affect coagulation either by non-specific inhibition of fibrin polymerization by the paraprotein, which can occur in myeloma, Waldenström's macroglobulinaemia and other lymphoproliferative disorders or by the paraprotein having specific activity against one or more of the proteins of the coagulation cascade. This is a relatively rare phenomenon, but activity against factor VIII, giving acquired haemophilia, and von Willebrand factor, giving acquired von Willebrand's disease, is recognized.[12]

Vascular disorders

In these disorders (Table 29.4), coagulation tests and platelet number and function are normal. The defect lies in the vascular endothelium and supporting tissues.[13] Senile purpura is relatively common and occurs on the extensor surfaces of the forearms and hands in particular. It is due to decreased amounts of collagen supporting the small blood vessels, which rupture with minor trauma or apparently spontaneously. The process is considerably accelerated by long-term treatment with corticosteroids. There is no specific treatment and, other than being cosmetically disturbing, it does not constitute a significant haemorrhagic diathesis. Hereditary haemorrhagic telangectasia is an autosomally dominantly inherited disease with multiple telangectasia of the lips, conjunctiva and the oral cavity associated with telangectasia throughout the gastrointestinal tract and also

Table 29.4 Haemorrhagic vascular defects.

Senile purpura
Steroid purpura
Hereditary haemorrhagic telangiectasia
Gastrointestinal angiodysplasia
Ehlers–Danlos syndrome
Henoch–Schönlein purpura

with pulmonary arteriovenous malformations. The condition tends to become progressively more severe with age and frequently presents in later life, usually as chronic iron deficiency anaemia. Troublesome gastrointestinal bleeding can usually be managed by iron supplementation but may require a chronic transfusion regimen. The fibrinolytic inhibitor tranexamic acid and estrogens have been used with some success. Owing to the widespread nature of the lesions, surgery is not usually a feasible treatment option.[14]

Scurvy (vitamin C deficiency) is associated with purpura and widespread bleeding, particularly from mucosal surfaces and subperiostally. It is due to both abnormal collagen synthesis and a defect in platelet function but is rare in the Western world, except in association with malnutrition and alcoholism. Amyloidosis may be primary or complicate paraproteinaemias, collagen vascular disorders and chronic infection. The deposition of amyloid protein in the blood vessels leads to fragility and consequently purpura is common. Cases of a specific coagulation defect due to absorption of the coagulation factor X by the amyloid protein have occasionally been reported. Ehlers–Danlos syndrome, especially type IV with a deficiency of type III collagen, results in structural weakness of major blood vessels with a tendency to rupture and consequent severe haemorrhage. Henoch–Schönlein purpura is rare in the elderly, being primarily a condition of childhood. It is an anaphylactoid purpura with cutaneous petechia and urticaria, associated with joint swelling, abdominal colic and melena. Despite the purpura, which is usually a manifestation of severe thrombocytopenia, the platelet count remains normal in this condition. Precipitating drugs should be withdrawn; steroids give relief from the joint and abdominal symptoms.

Thrombotic disorders

Although arterial thrombosis is a major cause of morbidity and mortality, its prevention is not possible at present; likewise, its pathophysiology is not well characterized. Smoking, hyperlipidaemia and a raised fibrinogen concentration are associated with accelerated atheroma, which accounts for the majority of arterial disease (*see* **Chapter 43, Peripheral arterial disease**). In addition, atrial fibrillation (*see* **Chapter 36, Arrhythmias**) and valvular cardiac defects are associated with arterial embolization, but a full understanding of arterial thrombosis does not exist at present.[15]

The situation with venous thrombosis is somewhat different and there have been rapid advances in the understanding, diagnosis and management of venous thrombosis (*see* **Chapter 44, Venous thromboembolism**) over the last few years. Venous thrombosis is primarily a disease of old age; until recently, it was thought that in the majority of cases the cause was circumstantial, with predisposing factors being immobilization and surgery, particularly to the hip, knee and pelvis, together with accessory factors such as obesity and malignancy. It has become clear, however, that in up to 50% of cases of venous thrombosis, there is an additional underlying genetic predisposition to thrombosis that becomes manifest under the above circumstances. The importance of thromboembolic prophylaxis of both surgical and medical patients at medium and high risk of developing thrombosis is increasingly being recognized and practiced. Likewise, the need for objective diagnosis of venous thrombosis by ultrasound examination or venography in the lower limb, and ventilation–perfusion lung scanning and pulmonary angiography in cases of suspected pulmonary embolus, has become established. Objective validation of the diagnosis of venous thromboembolic disease should always precede the initiation of treatment. Treatment should initially be with heparin, either unfractionated or low molecular weight heparin, and subsequently with oral warfarin. Warfarin in the elderly is not without hazards, there being an increased chance of drug interactions and in general the dose required in elderly patients is somewhat lower than in younger patients. Furthermore, the risk of bleeding is increased both at high INRs and also at normal INRs because of the increased incidence of underlying pathology, such as peptic ulcer, gastrointestinal malignancy and angiodysplasia. Consequently, it is important that recommended target ranges and duration of anticoagulation are adhered to and patients are not anticoagulated without good cause (Table 29.5).[16]

Thrombophilia

The proteins of the natural anticoagulant pathway act to limit and regulate thrombin generation. Deficiency of these proteins results in increased thrombin generation and consequently increased fibrin formation and venous thrombosis (Table 29.6). Deficiencies of antithrombin, protein C and protein S are rare but significant conditions do exist. They are autosomally dominantly inherited and only occur in the heterozygous form, the homozygous form being incompatible with life. These conditions usually present with venous thrombosis, which may be unusually widespread or occur at an unusual site, sometimes occurring spontaneously but often following a recognized predisposing factor. They may

Table 29.5 INR ranges in various conditions.

INR	Clinical state
2.0–2.5	Prophylaxis of deep vein thrombosis including surgery on high-risk patients
2.0–3.0	Treatment of deep vein thrombosis
	Pulmonary embolism
	Systemic embolism
	Prevention of venous thromboembolism in myocardial infarction
	Mitral stenosis with embolism
	Transient ischaemic attacks
	Atrial fibrillation
3.0–4.5	Recurrent deep vein thrombosis and pulmonary embolism
	Arterial disease including myocardial infarction
	Mechanical prosthetic heart valves

Table 29.6 Thrombophilic conditions.

Antithrombin – quantitative deficiency or qualitative dysfunction
Protein C – quantitative deficiency or qualitative dysfunction
Protein S – deficiency of total or free protein S
APCR resistance/factor V Leiden
Prothrombin 20210A allele
Antiphospholipid syndrome (lupus anticoagulant)

be recurrent and there is often a positive family history of venous thrombosis. Although patients may well present at a younger age, they can be diagnosed at any age and certainly second or recurrent episodes of thrombosis will occur in old age. The diagnosis of these conditions can be somewhat problematic as the concentrations of all these proteins fall during active thrombosis, and antithrombin levels fall during heparin therapy, while protein C and S levels fall during warfarin therapy.

Consequently, patients should ideally be investigated when they have neither active thrombosis nor are on anticoagulants. The finding of a deficiency state should lead to family screening as other family members are at risk. In the absence of a first episode of thrombosis, management should consist of adequate thromboprophylaxis at times of increased risk, such as surgery and immobilization. After a first episode of thrombosis, reasonable management is to anticoagulate for 3–6 months with warfarin with a target range of 2–3; after recurrent thrombosis, lifelong anticoagulation should be considered, initially with a target range of 2–3 but increasing this to 3–4 should further episodes of thrombosis occur while patients are already anticoagulated.[17]

A new thrombophilic defect of resistance to activated protein C (APCR) has recently been described. APCR is part of the natural anticoagulant pathway and usually acts to degrade activated factors V and VIII, thereby causing feedback inhibition of the coagulation cascade (Figure 29.2). Patients with APCR do not show the expected prolongation of the APTT following the addition of exogenous APCR and consequently have a low-activated protein C ratio. It has been shown that the basis of this defect is a single base substitution at position 1691 of the factor V heavy chain, resulting in a substitution of the amino acid glutamine for an arginine residue. This abolishes an APCR cleavage site and results in a factor V molecule that can be activated by thrombin but can no longer be inactivated by APCR; consequently, there is enhanced and prolonged activation of the coagulation cascade, increased thrombin generation and hence a predisposition to thrombosis. This condition can therefore be diagnosed both by a plasma assay and by genetic analysis of the factor V gene. The condition is autosomally dominantly inherited and is extremely common, occurring at an incidence of between 2 and 10% in the Caucasian population, although it appears to be rare or absent in non-Caucasian populations. Unlike the other thrombophilic conditions, individuals with both heterozygous and homozygous forms of this condition exist and the lifelong incidence of thrombosis appears to be somewhat less than antithrombin, protein C and S deficiency. Indeed, a significant proportion of patients with this condition may never have a thrombotic event. The frequency with which

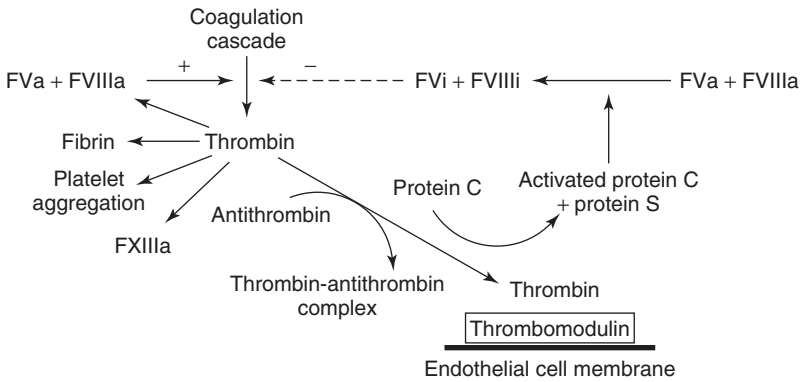

Figure 29.2 The natural anticoagulant pathway directly inhibits and negatively regulates the formation of thrombin by the coagulation cascade.

it occurs within the Caucasian population suggests that in evolutionary terms it must have some, as yet obscure, evolutionary advantage, but with life expectancy increasing and surgery becoming more frequent nowadays, it is clear that this condition is a major predisposing factor contributing to venous thrombosis. Indeed, between 40 and 60% of patients having a first episode of thrombosis have this condition, a 12-fold increase over the incidence within the background population. Although still not fully validated, management should parallel the management of other hereditary thrombophilic conditions.[18]

Lupus anticoagulant

The lupus anticoagulant is a laboratory diagnosis based on the finding of a prolonged APTT that is not due to a deficiency of a specific coagulation factor or a specific inhibitor of any coagulation factor, but to an autoantibody apparently directed against phospholipids, but in reality directed primarily against proteins that are intimately associated with phospholipids. Since the reactions of the coagulation cascade are phospholipid dependent, these antiphospholipid antibodies decrease the efficiency of the coagulation cascade and prolong the clotting time. The diagnosis can be confirmed using the dilute Russell viper venom test (DRVVT), in which the test is optimized so that phospholipid availability is rate limiting and this accentuates the effect of antiphospholipid antibody. Confirmation is achieved by showing that the clotting time returns to normal when excess phospholipid (in the form of freeze-fractured platelets) is added to quench the antibodies and that the test is not corrected by the addition of normal plasma that contains only additional coagulation factors.

The name lupus anticoagulant is somewhat unfortunate. The lupus refers to systemic lupus erythematosus (SLE) and it was in patients with this condition that the phenomenon was first observed. However, it has subsequently become clear that the majority of patients do not have SLE. Likewise, although it appears to be anticoagulant *in vitro* by prolonging the activated partial thromboplastin time (APTT), *in vivo* some lupus anticoagulants are associated with an acquired predisposition to thrombosis and bleeding does not occur. Consequently, the finding of a lupus anticoagulant may be an indication for thromboprophylaxis or even anticoagulation.

The significance of the finding of a lupus anticoagulant can be very variable. Transiently positive tests frequently occur after infections and many drugs can precipitate these antibodies, as can chronic infection such as syphilis. In these circumstances, the antibody does not appear to be associated with an increased incidence of either arterial or venous thrombosis. In patients with an underlying collagen vascular disease or in whom a primary antiphospholipid syndrome is diagnosed, there is an association between the finding of a positive test and recurrent arterial or venous thrombosis. The primary antiphospholipid syndrome consists of a positive lupus anticoagulant test and an association with livedo reticularis, thrombocytopenia and recurrent miscarriages in females. The lupus anticoagulant can precipitate both arterial and venous thrombosis and, within an individual, the site of second and subsequent thrombosis tends to occur in the same system; these patients may require long-term anticoagulation. There is no evidence that the antibodies causing the prolongation of the APTT *in vitro* are those that cause thrombosis; indeed, they may be an epiphenomenon, as a wide range of autoantibodies are found in these conditions, including antibodies against cardiolipin, which can be IgG or IgM, and are detected by a solid-phase enzyme-linked immunosorbent assay (ELISA).[19]

Key points

- Bleeding can be due to disorders of the coagulation cascade, platelets or blood vessels.
- Bleeding disorders can be congenital or acquired, the latter being more common.
- Drugs are a common cause of bleeding disorders.
- Thrombin disorders, both arterial and venous, are common in the elderly.
- Recurrent, severe or unusual episodes of venous thrombosis suggest thrombophilia.

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CHAPTER 30

Disseminated intravascular coagulation

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Introduction

Disseminated intravascular coagulation (DIC) is a failure of haemostatic homeostasis (Figure 30.1). The haemostatic system comprises five components: the coagulation cascade, the fibrinolytic cascade, platelets, the natural anticoagulant pathway and vascular endothelial cells. It is a complex system which normally maintains blood fluidity when blood is confined within the intravascular vessels, but is able to trigger rapid and localized coagulation if vascular integrity is breached. The intravascular space usually contains no exposed tissue factor but all cells outside the vascular system express tissue factor in their cell membranes which initiates coagulation through the extrinsic pathway. In DIC there is unregulated and uncontrolled activation of the coagulation cascade and platelets resulting in blockage of the microvascular system of critical organs. Simultaneously, there is activation of the fibrinolytic cascade generating plasmin and consequently fibrin and fibrinogen degradation, together with depletion of components of the natural anticoagulant pathway which contribute to the systemic bleeding diathesis.[1,2] Hence the paradox of DIC is that the clinical manifestations are of bleeding while the patient suffers serious morbidity and mortality due to organ damage due to microvascular thrombosis. DIC usually has an acute onset with bleeding manifestations dominating the clinical picture; however, a chronic form can occur, the manifestations of which are very different, usually with presentation as thrombosis, and the management of this form of condition likewise differs.

Pathophysiology

DIC is a pathophysiological syndrome characterized by clinical manifestations of generalized bleeding together with laboratory features of severe coagulopathy. It is not a discrete pathological entity but a final common pathway for a variety of triggers and precipitating factors and can be initiated by a number of different mechanisms (Table 30.1). DIC is characterized by great variation both between patients and within the same patient over time. It is a dynamic condition that will progress if untreated but can rapidly improve if appropriate treatment of the underlying cause and support haemostatic factors is given. Consequently, it has been difficult to perform adequate randomized controlled trials in the management and treatment of DIC, although there have been several recent advances in its early diagnosis and treatment.[3]

The primary triggers of DIC in the elderly are sepsis and malignancy, particularly disseminated malignancy. Other causes include massive trauma and major surgery, and ABO-incompatible blood transfusions and snake bites are rarer but recognized causes. DIC may be precipitated by activation of the coagulation cascade following tissue factor exposure, for example, as in massive trauma and major surgery; activation of the fibrinolytic cascade, for example, the liberation of plasminogen activators by leukaemic blasts in acute promyelocytic leukaemia or carcinoma of the prostrate; intravascular platelet activation, for example, heparin-induced thrombocytopenia; and by endotoxins in Gram-negative sepsis and meningococcal septicaemia or by direct proteolytic cleavage of circulating haemostatic proteins, as occurs in pancreatitis and with some snake venoms (Table 30.1). In addition to uncontrolled activation of the platelets and the coagulation cascade, there is depletion of the proteins of the natural anticoagulant pathway. Depletion of these further enhances the microvascular thrombosis and also leads to activation of the complement system, resulting in an inflammatory response and generation of vasoactive peptides, such as bradykinin. DIC also provokes a poorly characterized neuroendocrine response involving elevated catecholamines and glucocorticoids.[4]

Clinically, DIC manifests as simultaneous bleeding and microvascular thrombosis leading to multiple organ dysfunction including renal failure and adult respiratory distress syndrome (ARDS) and is often associated with fever, hypotension, acidosis, hypoxia and proteinuria. While bleeding is the most obvious and commonly

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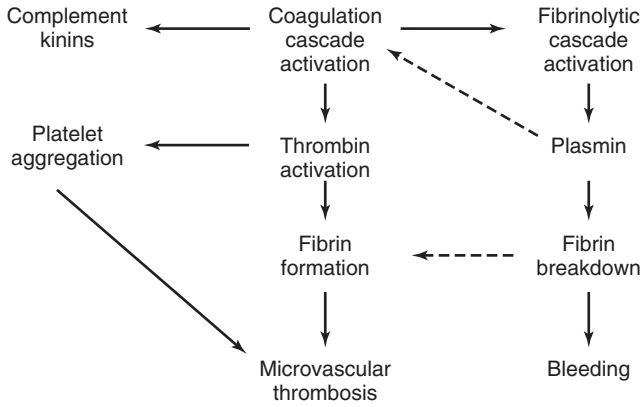

Figure 30.1 Mechanism of microvascular thrombosis and bleeding in DIC. Broken lines indicate inhibition.

Table 30.1 Mechanisms and precipitating factors in DIC.

Mechanism	Example
Coagulation cascade activation	Tissue factor exposure in trauma and extensive surgery
Fibrinolytic cascade activation	Plasminogen activators liberated in acute promyelocytic leukaemia
Intravascular platelet aggregation	Haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura
Endothelial cell activation	Gram-negative sepsis, malignancy
Direct proteolytic cleavage of haemostatic proteins	Pancreatitis, snake venoms

recognized manifestation, death by exsanguinations is rare due to the appropriate use of blood and platelet transfusions. The usual cause of death in DIC is multiorgan failure as a consequence of the microvascular thrombosis, which is not so clinically obvious. Treatment of multiorgan failure, which is a consequence of anoxia and ischaemic necrosis of vital organs, is far more difficult to treat satisfactorily.[5]

The bleeding in DIC is multifactorial in origin as a result of depletion of fibrinogen and all coagulation factors as a consequence of consumption due to uncontrolled and excessive activation of the coagulation cascade, diminished platelet number due to consumption and an additional or acquired platelet defect consequent to a proteolytic degradation of platelet surface glycoproteins and partial degranulation of α and dense platelet granules. Hyperfibrinolysis leads to elevated levels of fibrin and fibrinogen degradation products (FDP and D-dimers) which act as competitive inhibitors of fibrin polymerization. The uncontrolled generation of free thrombin and plasmin degrades fibrin, fibrinogen and coagulation factors, particularly factors V and VIII. Consequently, there is a systemic bleeding diathesis resulting in bleeding not only from local surgical incisions or traumatic wounds, but also generalized bruising, petechiae and purpura, together with bleeding from sites of venepuncture, arterial lines, drains, catheters and endotrachial tubes. There is also frequent gastrointestinal bleeding, haemoptysis, haematuria and even intramuscular or intracerebral bleeding. Excessive bleeding from a single site, particularly following surgery, is usually more indicative of failure of local haemostasis than DIC and requires specific local measures. The microvascular thrombosis results in anoxic damage and ischaemic infarction of vital organs, including lungs, kidneys, brain, pituitary, liver, adrenal, heart and skin.[6]

Diagnosis

The diagnosis of DIC is made in the presence of a predisposing cause, the clinical manifestations of systemic bleeding and multiorgan dysfunction and from appropriate laboratory investigations (Table 30.2). The haemoglobin is usually reduced owing to intravascular red cell fragmentation resulting in a microangiopathic haemolytic anaemia (MAHA) and there is profound thrombocytopenia. Coagulation times are abnormal with a prolongation of the activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) and depletion of fibrinogen, all due to consumption. In addition, there is evidence of fibrinolytic activation and fibrin degradation with elevations of serum FDPs or plasma D-dimers. In addition to these rapid and readily available tests, recent studies have shown that waveform analysis of the coagulation profile on automated machines can have both diagnostic and prognostic significance and laboratory abnormalities can be included in a validated scoring system for DIC. In addition to consumption of the coagulation factors and prolongation of the clotting times, levels of natural anticoagulant pathway proteins, namely, antithrombin, protein C and protein S, are also significantly reduced, contributing to the microvascular thrombosis.[7]

As DIC is a dynamic condition, it is preferable to perform the simple clotting tests frequently, both before and

Table 30.2 Laboratory diagnosis of DIC.

Test	Result
APTT	Prolonged
PT	Prolonged
TT	Prolonged
Fibrinogen	Low, usually $<1\ g\ l^{-1}$
Platelets	Low, usually $<50 \times 10^9\ l^{-1}$
FDPs	Raised
D-dimer	Raised

after clinical interventions, to judge their efficacy and the need for further blood product replacement therapy or interventions. The role of thromboelastography (TEG) and endogenous thrombin potential in monitoring DIC remains to be clarified. These tests are invariably abnormal but whether they can be used to direct interventional therapy is as yet unclear.

Management

The first principle of management of DIC should be towards resuscitation of the patient to achieve adequate oxygenation, blood pressure, circulation and renal perfusion. Once resuscitation is complete, then aggressive treatment of the underlying precipitating cause of the DIC should be addressed. Most frequently this is sepsis and aggressive broad-spectrum antibiotic therapy following the taking of appropriate microbiological samples is necessary. A few causes of disseminated malignancy, such as acute promyelocytic leukaemia and hormone-responsive breast and prostatic carcinoma, may also be amenable to treatment but the prognosis in DIC secondary to disseminated malignancy is usually poor; indeed, mortality overall remains high at 25–75% in various series.

There is considerable controversy about the place of blood product support in DIC. Clearly, red cells and platelet support, together with plasma product support, is indicated in patients who are actively bleeding. In patients who are not actively bleeding or requiring surgical or other intervention, the use of transfused clotting factors and platelets serves only to make the microvascular thrombosis worse unless the underlying precipitating factors have been treated. However, once these issues have been addressed and if the patient is bleeding, it is appropriate to transfuse red cells to achieve a haemoglobin of above $10\,g\,l^{-1}$ or haematocrit above 30%, to transfuse platelets to achieve a platelet count of $>80 \times 10^9\ l^{-1}$ to transfuse FFP ($10–15\,ml\,kg^{-1}$) to correct the PT and APTT to no more than 10% prolonged above the upper limit of normal and to increase the fibrinogen to $>1\,g\,l^{-1}$ through the appropriate use of cryoprecipitate (cryoprecipitate is particularly rich in fibrinogen) or fibrinogen concentrate. Following blood product intervention, the clotting screen should be repeated to assess the response to therapy and the need for additional future therapy.

In DIC due to sepsis, there is now evidence that depletion of the natural anticoagulant pathway proteins, such as antithrombin, protein C and protein S, contribute not only to microvascular thrombosis but also to the systemic inflammatory response and to a poorer prognosis. Activated protein C concentrate is licensed for use in severe sepsis and there is evidence in meningococcal meningitis that supplementation of depleted protein C improves outcome and recombinant human activated protein C is now licensed for use in severe sepsis with beneficial effects on mortality. The use of antithrombin concentrates is widespread in countries other than the UK but their efficacy has not yet been proven in an appropriate prospective randomized trial.

The use of heparin is even more controversial.[8,9] There are no adequate controlled trials to support its use and although it would appear logical to use an anticoagulant in a condition where the major morbidity and mortality are due to thrombosis, the use of a systemic anticoagulant in patients either with active bleeding or at high risk of catastrophic bleeding is troublesome. Furthermore, there are considerable problems in determining the duration of treatment and monitoring of heparin therapy in the presence of severely prolonged clotting times, and as heparin works by potentiating the activity of antithrombin, which is usually severely depleted in DIC, its efficacy is uncertain. Fibrinolytic therapy with tranexamic acid is contraindicated in DIC, unless the trigger mechanism is hyperfibrinolysis and the use of aprotinin, prostacyclin and antiplatelet drugs remains controversial and unproven. There is evidence that human recombinant activated FVIIa may be useful in uncontrolled life-threatening haemorrhage, but it should be recognized that the product is not licensed for this indication and its use in systemic bleeding disorders outside of haemophilia and platelet disorders is associated with a significant increase in arterial thrombotic events, particularly heart attacks and cerebrovascular accidents.

Chronic disseminated intravascular coagulation

Chronic DIC manifests very differently from acute DIC. The cause is usually, but not exclusively, disseminated malignancy, which may be manifest but may often remain occult for weeks or months after the initial presentation. Patients usually present with bruising from thrombocytopenia and on further investigation are found to have, in addition to thrombocytopenia, hypofibrinogenaemia and elevated FDPs or D-dimers. Bleeding is a rare manifestation of this condition, although bruising is common, while thrombosis in the form of superficial thrombophlebitis and deep venous thrombosis is common. Furthermore, a sterile nonbacterial endocarditis is well recognized, which can result in presentation with arterial embolization.[10]

Thus, the hallmarks of this condition are arterial and venous thrombosis rather than bleeding. The condition will usually resolve if the underlying cause can be successfully treated. If it cannot, the cautious application of anticoagulation rather than blood product support is the mainstay of treatment. Warfarin is notoriously difficult to use in this condition and low molecular weight heparin is the treatment of choice, in terms of both efficacy and improving overall outcome.

Key points

- DIC presents with haemorrhage, but it is the microvascular thrombosis that causes the multi-organ damage.
- DIC is commonly due to sepsis or disseminated malignancy.
- Diagnosis requires a blood count and a clotting screen.
- Treatment should address the underlying cause first, especially if sepsis, and only then may blood product support be indicated.
- Chronic DIC presents with thrombosis, rather than haemorrhage.

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CHAPTER 31

Anticoagulants

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Introduction

Thromboembolism in the arterial and venous circulation is more frequent with increasing age. The elderly are also more likely to have conditions such as colonic neoplasms and peptic ulcers that make them more susceptible to bleeding with anticoagulant therapy. Because of age-related changes in cardiovascular and renal homeostasis and concomitant (often multiple) medical problems, they do not tolerate haemorrhage well. They are more sensitive to anticoagulants such as warfarin. It is also likely that chronological age itself is associated with increased risk of anticoagulant-associated bleeding. This chapter will discuss the benefits/risks and methods to optimize anticoagulant therapy in the elderly.

The elderly are more prone to thromboembolism

The elderly are more prone to arterial as well as venous thromboembolism, and thrombotic disease is the commonest cause of hospital admission, disability and death in patients over 50 years of age in the developed world.

The incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) and thus venous thromboembolism (VTE) increases with increasing age. Between 65 and 69 years of age, annual incidence rates per 1000 for DVT and PE are 1.3 and 1.8 respectively, and rise progressively to 2.8 and 3.1 in individuals aged between 85 and 89 years. PE is more likely to occur in older men than women of similar age. About 1.7% of older people develop PE and 8% develop recurrent PE within one year of treatment for DVT.[1] The diagnosis of PE is often missed in elderly people and it is more often diagnosed only after death.[2]

The elderly are particularly likely to have concomitant conditions that substantially increase the risk of VTE. Thus the incidence of hip fracture increases from 116 (women) and 0 (men) per 100 000 person-years in the 60–64 year age group to 2597 (women) and 1187 (men) per 100 000 person-years in the 85+ year age group. The elderly are about eight times more likely to develop VTE in hospitals, nursing homes or other chronic care facilities. About 3% of patients with DVT and 21% of those with PE die in hospital. One-year mortality associated with DVT is 21% and that with PE is 39%. Elderly patients are more likely to have a new DVT at the time of admission to hospital with an acute non-surgical illness.[3,4]

As a result of the factors described above, the effective prevention of this common and life-threatening condition could produce major benefits. In 2005, the UK House of Commons reported that more than 25 000 patients in England died every year from VTE acquired in hospital; which is more than the combined annual total of deaths from breast cancer, AIDS and traffic accidents, and more than twenty-five times the number who die from MRSA each year.[5]

In the arterial circulation, the risk of thrombosis and embolism also increases with increasing age. Thus, thrombotic and embolic strokes are more frequent with increasing age. One reason for this is that non-valvular atrial fibrillation (AF) is much more common in the elderly and is associated with a fivefold increased risk of stroke.[6] The prevalence of AF rises from 0.5% in the fifth decade of life to 8.8% in the eighth.[6] Such individuals who do have an acute stroke are two- to threefold more likely to die than those with acute stroke who are in sinus rhythm.[7] The association with age is sufficiently important that the three commonly applied risk algorithms used to consider the risk–benefit of antithrombotic therapy in AF (CHADS2, NICE and ACCOP) all incorporate age >75 years into the risk calculation.[8]

Over 100 years ago, Virchow identified three main factors for development of thrombosis. The first was reduction in blood flow, which may be a factor in heart failure, a condition seen more frequently in the elderly. The second factor was changes in the vessel wall, which occurs with

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atherosclerosis and therefore with increasing age. Finally, changes in blood coagulability were cited by Virchow. Increases in clotting factor concentration, in platelet and clotting factor activation and a decline in fibrinolytic activity are all seen in the elderly.[9]

Anticoagulant response differs in the elderly

Several studies have confirmed the original findings of Eccles that oral anticoagulant requirements decline with age.[10] In one study, Routledge and co-workers showed that warfarin requirements fell with increasing age so that patients aged less than 35 required a mean of 8.1 mg per day, more than twice as much to maintain the same international normalized ratio (INR) as in patients aged 75 years or over. The relationship between age and warfarin requirements was rather weak, however, indicating that other factors may be more important in determining warfarin dose than chronological age itself.[11] These findings have been confirmed in a retrospective longitudinal study in 104 patients aged between 31 and 74 years when warfarin was started and followed for a median of 10 years. This suggests that the decline in dose is not related to a birth cohort effect but does occur in individuals as they grow older.[12] The average decline in dose (1.4% per year) in the study was very similar to the rate of decline observed in the much larger cross-sectional study discussed earlier.[11]

A similar reduced dose requirement in the elderly has also been reported with other coumarin anticoagulants such as acenocoumarol, bishydroxycoumarin and phenprocoumon. The reason for the increased sensitivity to oral anticoagulants is still not fully known, although most studies indicate a pharmacodynamic sensitivity rather than any major change in the pharmacokinetics of warfarin.[13,14] However, one study has reported an age-related decline in warfarin clearance.[15]

Increased age was also associated with an increased risk of haemorrhage in patients receiving unfractionated heparin (UFH) therapy intravenously with age greater than 70 years being associated with a significant increased risk of major bleeding.[16] It is not known what contribution pharmacokinetic and pharmacodynamic differences make to this increased risk. Low molecular weight heparins (LMWHs) are predominantly eliminated by renal excretion, which on average declines with increasing age. Age appears to be one factor predicting the occurrence and severity of bleeding or major bruising events in association with the widely used LMWH, enoxaparin, when given in therapeutic doses for the treatment of thromboembolic disease.[17] However, the manufacturers state that no dosage adjustments are necessary in the elderly unless kidney function is impaired.

Two new oral antithrombotic agents, dabigatran etexilate (an orally active inhibitor of both free and clot-bound thrombin) and rivaroxaban (an orally active inhibitor of both the 'free' and prothrombinase complex-bound forms of activated factor X) have received marketing authorization in Europe for the prevention of thromboembolic events following major orthopaedic surgery (e.g. total hip and knee replacement). Both are cleared in significant part by renal elimination (around 80% and 65% respectively), and as stated earlier, renal function does decline overall in the elderly. The manufacturers of dabigatran (but not rivaroxaban) recommend a reduced dose in patients aged over 75 years.[18]

The elderly are more prone to haemorrhage

The elderly are more prone to develop haemorrhage, even when not receiving anticoagulants. Life-threatening haemorrhage is most likely to occur in the gastrointestinal tract or intracranially. Although duodenal ulcer is more common at younger ages, gastric ulcer and gastrointestinal bleeding due to non-steroidal anti-inflammatory drugs (NSAIDs) are both more common with increasing age. In addition, the mortality from gastrointestinal bleeding is higher in the elderly. Intracranial bleeding (intracerebral and subdural) in the absence of anticoagulant therapy is also more frequent in the elderly.

Schulman has comprehensively summarized the increasing body of evidence indicating that age is an independent risk factor for major bleeding in patients receiving oral anticoagulant therapy with an average twofold increase in major bleeding among the elderly.[19]

Increased age also appears to be a risk factor specifically for intracranial haemorrhage. A case-control study compared 170 patients (median age, 78 years) with non-valvular AF who developed intracranial bleeding while on warfarin with 1020 matched controls (median age, 75 years) who were also receiving warfarin for non-valvular AF but did not develop intracranial bleeding.[20] The risk of intracranial bleeding was found to be increased in patients aged 85 years or over (adjusted odds ratio, 2.5; 95% CI, 1.3–4.7) and at INRs between 3.5 and 3.9 (adjusted odds ratio, 4.6; 95% CI, 2.3–9.4).The odds ratio for intracranial bleeding increased to 8.8 (95% CI, 4.6–17) at INRs greater than 4 but INRs less than 2 were not associated with a decreased risk (adjusted odds ratio, 1.3; 95% CI, 0.8–2.2). The incidence of bleeding in the elderly has been shown to be higher in the first 90 days of anticoagulation both due to poor control of anticoagulation and unmasking of an occult lesion.[21,22]

However, the incidence of intracranial bleeding in patients receiving oral anticoagulant therapy is still very low. Meta-analysis of six AF trials of warfarin versus placebo, involving 2900 patients, showed an intracranial

bleeding rate of 0.3% per year during anticoagulation and 0.1% per year in association with placebo.[23] Intracerebral haematomas account for 70% of intracranial bleeds associated with anticoagulation and are associated with a mortality rate of up to 60%. Most of the remaining episodes are subdural haematomas, which are less often fatal. The elderly are more likely to have cerebrovascular disease, leukoaraiosis and cerebral amyloid angiopathy which increase the risk of intracerebral bleeding. Poor mobility may predispose the elderly for recurrent falls that may increase the risk of both subdural and intracerebral bleeding.

The elderly are more likely to be on multiple drugs that may interact with warfarin, increasing the risk of bleeding. Particular agents include NSAID drugs, including aspirin, which markedly increase the risk of gastrointestinal bleeding when co-administered with warfarin. The nearly 13-fold increase in the risk of developing haemorrhagic peptic ulcer disease in concurrent users of oral anticoagulants and NSAIDs aged over 65 years is much greater than the sum of the risks of the same problem with each of these groups of medication used separately. The use of antiplatelet drugs (e.g. aspirin or clopidogrel) also increases risk hospitalization for major bleeding among users of coumarins.[24]

An Outpatient Bleeding Risk Index has been shown to be successful in classifying patients into low-, intermediate- and high-risk groups.[25] The index included four risk factors for major bleeding (attracting 1 point each in the index): age over 65 years, history of gastrointestinal bleeding, history of stroke, and one or more specific comorbid conditions (recent myocardial infarction, haematocrit of less than 30%, presence of diabetes mellitus and serum creatinine of greater than 1.5 mg dl^{-1}). A score of zero indicated low risk, 1–2 was classified as medium risk and a score of 3–4 was suggested to indicate high risk (23% in 3 months and 48% in 12 months). Although this may be a potentially useful tool in some circumstances, it automatically places all people aged over 65 years in the medium-risk category, which we believe is not always the case. It is important to recognize that under-usage of anticoagulants should not be encouraged in elderly patients, since treatment has been shown to be highly effective in this group (see below).

Anticoagulants are effective in the elderly

Heparin and warfarin are as effective in elderly patients as they are in younger ones in the treatment of venous thromboembolism. A fixed oral dose of dabigatran (150 mg bid) in patients with acute VTE (age range 18–93 years, median 56 years), has been shown to have similar efficacy and safety as warfarin.[26]

Six studies of oral anticoagulation for the prevention of thromboembolic events in patients with non-valvular AF, have shown a reduction in events in patients over a wide age-range.[23] Adjusted-dose warfarin reduced stroke by 62% (95% CI, 48–72%). The absolute risk reduction for primary prevention was 2.7% per year and 8.4% per year for secondary prevention. The Danish AFASAK Study included subjects with AF who were aged between 38 and 91 years, in whom anticoagulant therapy reduced the relative risk of stroke by 54%.The Boston Area Anticoagulation Trial showed an 86% reduction in stroke in an elderly population (mean age 68 years). A mixed retrospective and prospective cohort study of 13 559 adults with non-valvular atrial fibrillation has reported that adjusted net clinical benefit of warfarin therapy was greatest for patients who were over 85 years of age (2.34% per year; 95% CI, 1.29–3.30%).[27]

More recently, the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) assigned 973 patients aged 75 years or over (mean age 81.5 years, SD 4.2) with AF randomly to warfarin (target INR 2–3) or aspirin (75 mg per day). There were 24 primary events (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in people assigned to warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in individuals assigned to aspirin. This supports the view that the benefits of warfarin over aspirin therapy remain in the elderly and were not offset by an increased risk of intracranial haemorrhage.[28]

One study in patients with AF (mean age 71 years) has shown dabigatran at a dose of 110 mg to be associated with similar rates of stroke and systemic embolism, lower rates of major haemorrhage and at a dose of 150 mg, to be associated with lower rates of stroke and systemic embolism but similar rates of major haemorrhage as compared with warfarin.[29]

The risk–benefit equation: how to optimize it in the elderly

The most important factors associated with risk of bleeding while on anticoagulants are: (a) degree of anticoagulation; (b) the presence of potential bleeding site; and (c) duration of anticoagulant therapy.

Degree of anticoagulation

As discussed previously, several studies have reported a curvilinear relationship between the degree of anticoagulation and the risk of bleeding (Figure 31.1).[30] Thus the bleeding risk rises threefold between INRs 2 and 3 and a further three fold between 3 and 4.[21] Since a high INR is one of the most important factors determining the bleeding risk, dwarfing any possible age-related effects, it is essential that the lowest effective intensity of anticoagulation is maintained in the elderly.

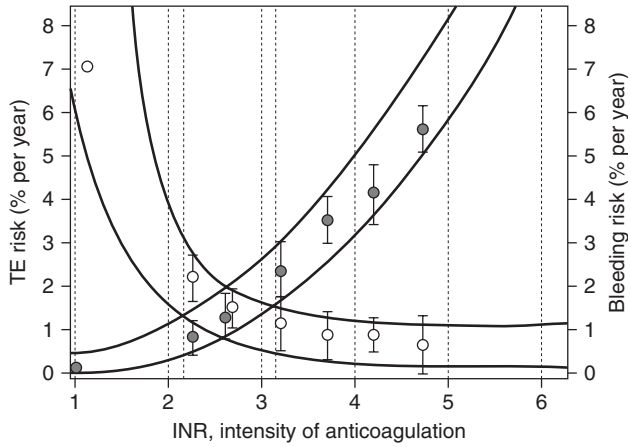

Figure 31.1 Relationship between intensity of anticoagulation and risk of thromboembolism (TE) and bleeding in 1865 patients receiving oral anticoagulants after insertion of St Jude prosthetic heart valves. The single open circle represents 12 patients who received only antiplatelet agents because of contraindications to warfarin therapy. INR = international normalization ratio. Reproduced from Horstkotte *et al.*[30] by permission of *The Journal of Heart Valve Disease*.

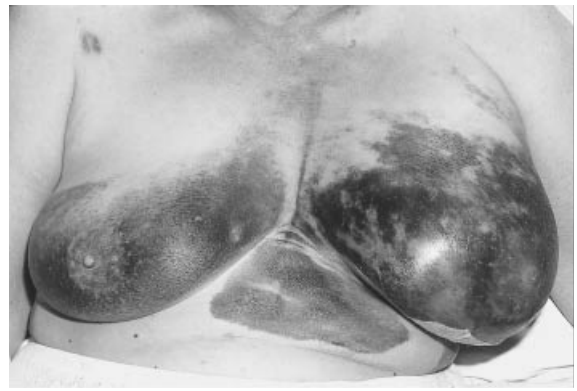

Figure 31.2 Severe bleeding into the breasts of a 70-year-old lady receiving warfarin after insertion of a prosthetic heart valve. More than 500 ml of blood was drained from the left breast and she was eventually controlled carefully between an INR of 2.5 and 3.0 without recurrence of bleeding.

In major studies of primary stroke prevention in non-valvular AF, target INRs ranged from 1.5 to 4.5. There was no evidence that the most intensive anticoagulation reduced stroke risk more and it may well have increased bleeding risk. The higher intensities of anticoagulation used in the past may well have contributed to the reports of higher incidence of anticoagulation-related bleeding. The recommended ranges of anticoagulation for many indications have fallen over the recent years and this should improve the safety of anticoagulant therapy. A target INR of 2.5 is therefore recommended for treatment of venous thromboembolism, primary and secondary stroke prevention in individuals with non-valvular AF.[31] A higher intensity of anticoagulation may be needed under specific circumstances, such as prevention of thromboembolism in those with prosthetic heart valves, or those with recurrent thromboembolism.

Presence of potential bleeding site

When bleeding occurs, it is usually from a pathological site, often in the bladder or bowel, or from an abnormal intracranial blood vessel. Even in apparently spontaneous bleeding, for example into the skin, this may be related to the atrophic changes that occur with increasing age (Figure 31.2). As has been mentioned earlier, some episodes of haemorrhage may result in the discovery of potentially remediable (including malignant) lesions at an earlier stage than would otherwise have occurred. Certainly *all* patients who bleed should be investigated for underlying pathology, even if the bleeding episode occurred when the INR was excessive. Clinicians should also consider the possibility of occult bleeding in any patient with unexplained symptoms or signs while receiving warfarin. Alveolar haemorrhage may present with unexplained anaemia or dyspnoea, for example. Other presentations that may pose diagnostic difficulties include retroperitoneal haemorrhage, rectus sheath haematoma and spontaneous intramural intestinal haematoma (which may present as small intestinal obstruction).

Duration of anticoagulant therapy

Many elderly patients are prescribed warfarin for stroke prevention in non-valvular AF or to prevent thromboembolism from a prosthetic heart valve. Both these situations require long-term anticoagulation. A duration of three months is recommended for treatment of first episode of unprovoked (idiopathic) DVT and PE.[31] Long-term anticoagulation is recommended in patients with recurrent DVT or PE. The decision about the duration of anticoagulation in a given patient will be dictated by the specific clinical circumstances in that particular individual.

The risk of bleeding continues as long as an individual is on anticoagulant therapy. As discussed earlier, the risk of bleeding is higher during the initial weeks and months of anticoagulation. One study, which included 712 patients with venous thromboembolism, found that the overall risk of serious haemorrhage was six per 1000 patient-months; all but nine such episodes occurred in the first month and none in the next two months.[32] This early occurrence of a significant proportion of major haemorrhage is supported by other studies.[21,22] Therefore, older patients need closer monitoring during the first month of anticoagulation.

Perhaps the most difficult time is during initiation of anticoagulants. Because of their sensitivity to warfarin,

the elderly may be excessively anticoagulated at this time, particularly if standard rather than tailored induction doses are used. The original tailored regimen[33] used a first dose of 10 mg, adjusted thereafter according to the INR, which was measured daily. Siguret and colleagues have since devised a regimen for patients aged over 70 years.[34] This involved giving 4 mg daily for three successive days and was shown to be safe and accurate in elderly hospitalized patients.

Conclusions

Anticoagulants are now widely used in elderly patients. The view that they are lethal drugs in the elderly has been shown to be unjustified.[35] The introduction of INR, downward revision of therapeutic ranges and the production of guidelines for initiation and maintenance therapy have helped to improve the risk–benefit equation positively.[33] The use of computer-assisted anticoagulation and near-patient INR testing have improved monitoring of anticoagulation even further. Newer oral anticoagulants such as dabigatran and rivaroxaban appear to be similar to warfarin in terms of efficacy and safety. Other oral anticoagulants are currently under investigation.

Education of patients and carers on important aspects of anticoagulant therapy is likely to improve the control of anticoagulation and compliance. A small study of compliance (adherence or concordance) found no decline in compliance in elderly ambulant patients.[36] A combined retrospective and prospective cohort study, which included 323 patients aged over 80 years on oral anticoagulant therapy, found that the rate of major bleeding was 2.4 events per 1000 patient-months.[37] This study found no association between an increased rate of bleeding and socioeconomic, cognitive variables or functional impairments. However, insufficient education in anticoagulant therapy as perceived by the patient or caregiver [odds ratio (OR), 8.83], polypharmacy (OR, 6.14), and INR values above the therapeutic range (OR, 1.08) were found to be significant predictive factors for bleeding complications.

A careful analysis of risk versus benefit in every patient before commencing anticoagulant therapy is likely to minimize the incidence of serious complications. Most importantly, careful monitoring to maintain the lowest effective INR, avoid dangerous drug interactions, and to detect and manage haemorrhagic complications promptly will further enhance the benefits of anticoagulants in the elderly.

Key points

- The elderly are more prone to venous and arterial thromboembolism.
- Ageing is associated with increased sensitivity to anticoagulants.
- Intracranial haemorrhage is more likely to occur in individuals aged 75 years or over.
- The risk of all haemorrhage is greatest in the first month after commencement of anticoagulation, but persists throughout the course of treatment.
- The risk of all haemorrhage increases disproportionately with increasing intensity of anticoagulation.
- Nevertheless, when they are used appropriately, anticoagulants are highly effective drugs in the elderly.

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CHAPTER 32

Myelodysplasia

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Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by dysplasia, ineffective haematopoiesis and potential risk of transformation into acute leukaemia.[1,2] These disorders are sporadic and arise *de novo* or may result following toxin, radiation and chemotherapy exposure (secondary MDS).[3,4] MDS primarily affects older patients, with an increased incidence with advancing age.[5,6] Disease onset prior to the sixth decade is uncommon, although not unheard of, especially with treatment-related or secondary MDS. As the demographics in developed countries shift towards older patient populations due to increased longevity and better quality of healthcare and more people are receiving intensive chemotherapy, the prevalence of MDS will likely increase.

MDS may easily be overlooked in elderly patients. It can present simply as a chronic macrocytic anaemia and there may be a tendency to 'leave well enough alone' in an older patient with multiple comorbidities. However, our understanding of MDS continues to improve and better treatment strategies have been developed which can prolong life and also delay transformation to acute leukaemia. Therefore, it is important to evaluate carefully any cytopenia in older patients.

Epidemiology and clinical presentation

The exact incidence of *de novo* MDS remains unclear but appears to be greater than the incidence of acute myelogenous leukaemia (AML).[7] In a recent analysis of the SEER database from 2001 to 2004, the age-adjusted incidence rate was 3.3 per 100 000.[8] A sharp increase in the incidence of MDS was observed with age: for those aged 80 years and older the incidence was five times that of those aged 60–69 years (35.5 compared with 7.1 per 100 000).[8] The age-adjusted incidence of MDS is slightly higher among males than females. However, these are likely underestimations of the true incidence of this disease owing to the underdiagnosis of MDS in the past. The incidence rate appears to have increased from 3.3 per 100 000 per year in 2001 to 3.56 per 100 000 in 2004.[9] This increase is probably due in part to an increasing population of people over age 65 years, and also increased recognition and diagnosis of the disease by haematologists and oncologists with the development of more effective therapies.

There are several well-known risk factors for the development of MDS, including exposure to organic solvents, ionizing radiation and prior chemotherapy. The incidence of therapy-related myelodysplasia is also increasing. Therapy-related MDS can result from prior exposure to ionizing radiation or chemotherapy. Prior exposure to alkylating agents is associated with the highest risk of MDS and has very distinct cytogenetic abnormalities, such as loss of the long arm of chromosomes 5 and/or 7. The risk for developing therapy-related MDS or AML has been described in long-term survivors of cancers treated with semustine (methyl-CCNU). The actuarial risk is between 6 and 9% in patients treated for Hodgkin's disease and 17% in patients treated for multiple myeloma. The risk of developing MDS increases with the use of regional radiation therapy following treatment for common cancers such as breast cancer, small cell lung cancer and testicular cancer. Topoisomerase II inhibitors, such as epipodophyllotoxins and anthracyclines, have also been associated with therapy-related AML, but usually without an MDS prodrome, and commonly involve chromosomal abnormalities such as 11q23, 3q26 and 21q22.[10]

The clinical presentation of MDS is varied. Symptoms for the most part are non-specific and depend upon the number and severity of cytopenias present. The majority of patients with MDS have a macrocytic anaemia with or without additional cytopenias. Patients with anaemia may have profound symptoms of dyspnoea on exertion, fatigue, lethargy, malaise, dizziness and even angina.[11] Neutropenic patients may develop severe systemic infections and infection represents a primary cause of death

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in many cases of MDS.[12] Increased infectious risk may be a result of neutrophil dysfunction secondary to impaired chemotaxis and/or microbial killing.[12,13] T-Cell function is thought to remain intact and therefore patients with MDS less commonly develop viral or mycobacterial infections in the absence of treatment with immunosuppressive agents.[12] Other symptoms may include easy bruising or bleeding, a common manifestation of thrombocytopenia and dysfunctional platelets.

The physical findings of MDS are likewise non-specific and usually reflect underlying cytopenias if present. Of note, patients with chronic myelomonocytic leukaemia (CMML) may have splenomegaly, an unusual finding in patients with other subtypes of MDS.

Diagnosis

Blood and bone marrow examination

MDS is diagnosed in patients with one or more cytopenias and depends upon the finding of dysplastic features within the bone marrow in one or more lineages. A peripheral blood smear is helpful in demonstrating a normocytic or a macrocytic anaemia, but alone is insufficient for diagnosis. In order to make the diagnosis, a bone marrow aspirate and biopsy are required. An aspirate is necessary to evaluate morphology, quantify the number of myeloblasts, and assess for cytogenetic abnormalities. A core bone marrow biopsy is used to assess the bone marrow cellularity, which is typically hypercellular and indicative of ineffective haematopoiesis in the setting of peripheral cytopenias.

The morphological features of red cell precursors in the bone marrow aspirate include megaloblastic (asynchronous maturation of the nucleus and cytoplasm) or binucleate or multinucleated cells. Ring sideroblasts may also be identified. These are red cell precursors with iron-laden mitochondria and are defined by the presence of five or more Prussian Blue-staining iron granules encircling more than one-third of the nucleus in more that 15% of the erythroblasts. Erythroid hyperplasia may also be prominent and is associated with ineffective erythropoiesis (a hallmark of MDS).

Abnormalities in the myeloid series can include a left shift with a predominance of immature myeloid cells, hypogranulation and hypolobulation of the nucleus in mature granulocytes. A classic finding is the presence of pseudo-Pelger–Huet cells, which are granulocytes with a bilobed nucleus in a *pince-nez* configuration. A typical feature in the bone marrow of MDS patients is the presence of >5% myeloblasts. The proportion of myeloblasts has both diagnostic and prognostic information (see below) and is important in differentiating AML from MDS.

The megakaryocytes may likewise be dysplastic and may have not only a quantitative but also a qualitative defect. Examination of the peripheral smear may reveal giant or agranular platelets. In the bone marrow, the megakaryocytes may be small and hypolobulated.

Dysplasia in the bone marrow is not sufficient to establish the diagnosis of myelodysplasia. Deficiencies of vitamin B_{12} and folate, hypothyroidism, viral infections such as Epstein–Barr and the human immunodeficiency virus and exposure to antibiotics and other chemicals such as ethanol, chemotherapy and benzene can result in dysplasia. These other causes must be ruled out systematically by a careful history and physical and laboratory examination.

Cytogenetics

A critical component of the bone marrow aspiration is the cytogenetic examination of the bone marrow, which not only may help to establish the diagnosis, but also yields important prognostic information (see below). Roughly 60% of patients with MDS have a normal karyotype, but the presence of a common cytogenetic abnormality may establish the diagnosis in difficult cases.[14] In addition, new cytogenetic abnormalities may document an evolution to a more clinically aggressive state (i.e. transformation to acute leukaemia). The sensitivity of cytogenetic analysis has been greatly increased by the utilization of fluorescent *in situ* hybridization (FISH), which uses specific DNA probes to identify rapidly individual chromosomes in hundreds of cells and does not depend upon cell division. The drawback of this approach is that the analysis is restricted to already known and well-established cytogenetic abnormalities.

One series found that cytogenetic abnormalities were more common in the advanced stages of MDS compared with the less advanced MDS subtypes.[15] The more common abnormalities are trisomy 8 and deletions of the long arms of chromosomes 5, 7, 11, 13 and 20. Complex karyotypes, defined as three or more cytogenetic abnormalities, are found in 15% of cases and confer a poor prognosis. [15,16] A sole abnormality involving deletion of 5q is seen commonly in patients with refractory anaemia and represents a distinct clinical syndrome, the '5q syndrome'. This syndrome, seen most often in elderly women, is characterized by a prolonged clinical course, which does not typically progress to acute leukaemia. The anaemia is typically profound, but neutropenia is usually mild and platelets are typically elevated. It must be understood that a normal karyotype does not exclude the diagnosis of MDS and is seen in approximately half of the cases of MDS.

Therapy-related MDS is also associated with specific chromosomal abnormalities. In particular, partial or complete loss of chromosome 5 or 7 have been seen after exposure to alkylator therapy, and patients exposed to topoisomerase II inhibitors typically present with a monocytic leukaemia without antecedent MDS and typically

have rearrangements of the mixed lineage leukaemia gene located on 11q23.[17]

Other genetic events

Over the past few years, our understanding of the genetic basis for MDS has expanded significantly. Pivotal work by Ebert *et al*. identified that haploinsufficicny of the ribosomal gene RPS14 cooperates with the loss of micro-RNAs miR-145 and miR-146 which result in key features of the 5q phenotype.[18] Mutations in the Ten-Eleven Translocation-2 gene (TET2) were recently identified in MDS and other myeloid neoplasms.[19–21] TET2 mutations occur in 10–26% of MDS patients. The enzyme converts methylcytosine to hydroxymethylcytosine and thus may play a role in DNA methylation and may predict response to hypomethylating agents.[22] Other recurrent mutations in RUNX1, ASXL1 and TP53 have also been discovered in a substantial proportion of MDS cases. Active investigation is ongoing to determine which of these mutations are causative in the pathogenesis of MDS and which play a role progression of the disease and or may be therapeutically relevant to predict response to therapy.

Classification

The current term MDS was adopted by the French, American and British (FAB) Cooperative Group in 1976 in their classification scheme of these disorders. The WHO classification was proposed as a modification of the FAB system.[23] Notably, the criterion for AML was lowered from 30% blasts in the bone marrow to 20% blasts, which eliminated the category of RAEB-t of the FAB classification. Patients with refractory anaemia (RA) with or without ring sideroblasts were divided based upon the presence of unilineage or multilineage dysplasia. Multilineage dysplasia has been shown to impart an inferior prognosis. The category of refractory anaemia with excess blasts was divided into two categories based upon the percentage of blasts. Furthermore, in this classification system MDS associated with a del(5q) was assigned its own category and is associated with a prolonged life expectancy. A new category, MDS-unclassifiable, was introduced to incorporate patients with significant unilineage dysplasia without meeting other criteria for the diagnosis. In addition, chronic myelomonocytic leukaemia has been removed from the MDS category and placed within the myeloproliferative neoplasms category. The WHO was updated in 2008 (Table 32.1).[24] Important changes include three categories of refractory cytopenia with unilineage dysplasia, RA, refractory neutropenia (RN) and refractory thrombocytopenia (RT), which reduced the number of cases referred to as unclassifiable.[24]

Prognosis

The WHO classification scheme is useful for the diagnostic categorization of patients with MDS, but these diagnostic groups represent heterogeneous patient populations with varied prognoses. Several prognostic systems have been devised to predict the outcome of individual patients better. The most widely used and accepted is the International Prognostic Scoring System, from the International Myelodysplastic Syndrome Risk Analysis Workshop[6] (Table 32.2). In this analysis based on over 800 patients, the important predictors for overall prognoses were cytogenetic abnormalities, percentage of myeloblasts in the bone marrow and the number of lineages that exhibited cytopenias. Favourable cytogenetics includes the loss of the Y, 5q or 20q chromosomes or the presence of a normal karyotype. Adverse cytogenetic changes were those with three or more cytogenetic abnormalities or any abnormalities involving chromosome 7. Number scores are attributed to each variable, thus dividing patients into four categories based on the sum of scores for each variable. The median survival for the categories were 5.7, 3.5, 1.2 and 0.4 years for the low-, intermediate-1-, intermediate-2- and high-risk groups, respectively[25] (Table 32.3). The time for 25% of the patients in each of the four risk groups to evolve into acute leukaemia was 9.4, 3.3, 1.1 and 0.2 years, respectively. This schema provides very useful prognostic information for patients and counselling regarding treatment options such as haematopoietic stem cell transplantation. However, the usefulness of the IPSS is limited by the fact that patients with secondary MDS were excluded from the analysis and the information only pertains to patients at the time of diagnosis and cannot be used to estimate the real-time risk for patients. Furthermore, it may underestimate the impact of cytogenetics. In this analysis, rare, non-complex cytogenetic abnormalities were placed in the intermediate-risk karyotype group.

Haase *et al*. reviewed the cytogenetic data for over 2124 patients with MDS in Austria and Germany.[16] Given the large number of patients, cytogenetic risk groups could be further refined. The median survival was 53.4 months for patients with normal karyotypes and 8.7 months for those with complex anomalies. Thirteen rare abnormalities were identified with good, intermediate and poor prognostic impact (Table 32.4).

In an attempt to incorporate dynamic variables such as transfusion burden, the WHO prognostic scoring system (WPSS) was developed.[26] This model takes into account WHO subgroups, karyotype and transfusion requirement to classify patients into five risk groups with variable median survivals (12–103 months) and also probability of leukaemia conversion. The advantage of the WPSS is that it is a dynamic prognostic scoring system which can be used for patients at any time during the course of their disease.

Table 32.1 2008 WHO Classification and Criteria of MDS.

Type	Peripheral blood	Bone marrow
Refractory cytopenias with unilineage dysplasia (RCUD) Refractory anaemia (RA) Refractory neutropenia (RN) Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia <1% or rare blasts	Unilineage dysplasia >10% of the cells in one myeloid lineage <5% blasts ≤15% of erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anaemia No blasts	Erythroid dysplasia only <5% blasts ≥15% ring sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Bi- or pancytopenia No/rare blasts No Auer rods Monocytes $<1000\,\mu l^{-1}$	Dysplasia in ≥10 % of cells in two or more myeloid cell lines No Auer rods ±15% ringed sideroblasts <5% blasts
RAEB-1 (refractory anaemia with excess blasts-1)	Cytopenias <5% blasts No Auer rods	Uni- or multilineage dysplasia 5–9% blasts No Auer rods
RAEB-2 (refractory anaemia with excess blasts-2)	Cytopenias 5–19% blasts Auer rods may be present	Unilineage or multilineage dysplasia 10–19% blasts Auer rods
MDS-U (MDS unclassified)	Cytopenias No or rare blasts	Unequivocal dysplasia in <10% of cells in one or more myeloid cell lines when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS No Auer rods <5% blasts
5q-Syndrome	Anaemia <5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobulated nuclei No Auer rods <5% blasts Isolated del(5q)

Adapted from *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, IARC Press, Lyon, 2008.[24]

Table 32.2 International Prognosis Scoring System (IPSS) in MDS.[6,25]

	Score				
Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5–10		11–20	21–30
Karyotype[a]	Good	Intermediate	Poor		
Cytopenias[b]	0/1	2/3			

[a]Karyotype definitions: good,–Y,–5q,–20q, normal; poor, chromosome 7 abnormalities or complex karyotypes (three or more abnormalities); intermediate, all others.
[b]Cytopenia definitions: haemoglobin, $<10\,g\,dl^{-1}$; absolute neutrophil count, $<1800\,\mu l^{-1}$; platelet count, $<100\,000\,\mu l^{-1}$.

It has been externally validated and demonstrated to be very helpful particularly for determining the prognosis of patients with low-risk disease.[27]

To overcome some of the limitations of the IPSS which excludes patients with t-MDS, proliferative chronic myelomonocytic leukaemia and those who have received prior therapy, a group at the University of Texas M.D. Anderson Cancer Center developed a new prognostic scoring system that included all of these patients.[28] This model was able to identify four prognostic groups based upon a prognostic score which included features such as age, performance status, platelet count, haemoglobin, white blood cell count, complex karyotype or chromosome 7 abnormality and prior transfusions.

Table 32.3 IPSS Survival for MDS and Evolution to AML.

Risk category	Score	Median survival (years) in the absence of therapy	25% AML progression (years) in the absence of therapy
Low	0	5.7	9.4
Intermediate-1	0.5–1.0	3.5	3.3
Intermediate-2	1.5–2.0	1.1	1.1
High	2.5	0.4	0.2

Adapted from Greenberg *et al.*[6]

Table 32.4 Prognosis of rare cytogenetic abnormalities.

Risk group	Cytogenetic abnormality
Good-prognosis cytogenetics	del(9q)
	+1/+1q
	t(1q)
	t(7q)
	del(12p)
	Chromosome 15 anomalies
	t(17q)
	Monosomy 21
	Trisomy 21
	–X
Intermediate-prognosis cytogenetics	del(11q)
	Chromosome 19
Poor-prognosis cytogenetics	Complex, all
	t(5q), NC
	4–6 abnormalities
	>6 abnormalities

NC, non-complex Karyotype.
Adapted from Haase *et al.*[16]

Treatment

The management of patients with MDS requires consideration of several variables, including comorbidities, patient age, severity of cytopenias and the fact that the older patient population in general do not tolerate or respond to conventional therapy. The treatment for MDS is divided into two categories, high and low intensity. High-intensity treatment in general requires hospitalization and includes intensive chemotherapy and haematopoietic stem cell transplant. In contrast, low-intensity treatments are defined as those which can be performed in an outpatient setting, including haematopoietic growth factors, differentiation agents, low-intensity chemotherapy and transfusion support. Key factors in determining high- versus low-intensity treatment are a patient's age, performance status and IPSS score. High-intensity therapies are usually considered for patients <60 years old, who have good performance status and who fall into the intermediate-2- or high-risk categories. High-intensity treatment may be considered for patients >60 years old who have good performance status and who are in the higher risk categories, but generally patients >60 years of age are considered for low-intensity therapy. Patients >60 years of age in the low- or intermediate-1-risk category are usually considered for supportive care or low-intensity therapy.

Supportive care

Transfusion support and iron overload

Supportive care is an integral part of the management of all patients with MDS regardless of risk category. Supportive care includes treatment with antibiotics for infection and transfusion support for anaemia and thrombocytopenia. In order to lessen isoimmunization, viral infections and febrile transfusion reactions, leukoreduced and irradiated products are encouraged. In some cases, patients may receive well over 50 units of packed red blood cells. With each unit of blood containing 250 mg of iron, patients may develop iron overload. High levels of iron may lead to secondary haemachromatosis and its resultant adverse hepatic, pancreatic, gonadal and cardiac effects.[29] Iron chelation with deferoxamine[30] may be administered to these patients; however, this therapy is difficult. Deferoxamine only chelates ~25 mg of iron per day, must be administered subcutaneously and can lead to chronic skin irritation and cataracts. Two oral iron chelators are now available, deferiprone and deferasirox. Deferiprone reduced hepatic and cardiac iron content in thalassaemia patients, but its utility in MDS is limited by the risk of agranulocytosis and it is not currently approved in the USA.[31] Deferasirox is administered once daily and is approved for secondary iron overload in transfusion-dependent anaemias. It has been tested in MDS and found to decrease serum ferritin significantly at 1 year in heavily transfused MDS patients, but exactly what impact that has on total body iron stores or even survival in MDS is unclear.[32] Side effects typically include mild nausea and diarrhoea and careful surveillance of renal and hepatic function should be done as nephrotoxicity and hepatotoxicty have been described. Furthermore, baseline hearing and vision tests are recommended prior to initiating the drug and yearly thereafter because of the risk of auditory and ophthalmological disturbances.

Several international guidelines on iron chelation for MDS have been published.[33–37] Many patients with MDS rarely live long enough to develop the complications of iron overload, hence iron chelation as a therapy should be reserved for those patients with lower risk disease with an expected survival of more than 1 year, which is fairly consistent across the various guidelines. Once patients have received anywhere from 20 to 50 units of red blood cells and if the serum ferritin is >1000–2500 ng ml^{-1}, the recommendation is to initiate iron chelation therapy.[31]

In addition to requiring periodic red blood cell transfusions, some patients with more advanced MDS may have severe chronic thrombocytopenia with associated bleeding. This can be life threatening if significant bleeding occurs in the brain or gastrointestinal tract. Platelet transfusions can be administered, but should be given judiciously as many patients become alloimmunized and then fail to respond to subsequent platelet transfusions.[38] Similarly to red blood cell transfusions, platelets should be irradiated.[38,39]

Erythroid-stimulating agents

Erythroid-stimulating agents (ESAs) are not approved by the FDA for MDS, but they are commonly used to treat MDS patients to reduce transfusion requirements. Recombinant erythropoietin (EPO) is given subcutaneously 1–3 times weekly. Darbopoietin-α (DAR) is a pegylated form of EPO and is given in doses of 150–300 μg per week. A meta-analysis compared treatment with EPO and DAR and concluded that the drugs have similar response rates in MDS patients.[40] The serum EPO level is usually elevated in MDS patients; nonetheless, ~25% of patients with MDS respond to treatment. ESAs tend to have the greatest effect in patients with low transfusion requirements, low baseline serum EPO levels and low- or intermediate-1-risk MDS without excess blasts.[41,42] Response to ESAs may take time. In one study, response rates more than doubled from 12 to 26 weeks, hence a long trial of the agent is generally required. The combination of EPO and granulocyte-colony stimulating factor (G-CSF) has been shown to increase the haematocrit and the number of circulating neutrophils and the combination may be synergistic. A predictive model for response can be utilized to identify patients who have a low, intermediate or high probability of responding to ESAs and G-CSF (Table 32.5). The combination of G-CSF and EPO appears to be particularly synergistic in patients with refractory anaemia with ring sideroblasts.[42–44]

Randomized trials have demonstrated an increased risk of thromboembolic complications and inferior survival in patients with solid tumours receiving ESAs.[45,46] Two independent retrospective analyses comparing MDS patients treated with ESAs with MDS patients not treated with ESAs have demonstrated a survival benefit for those treated with ESAs.[44,47] This benefit probably arises because of they minimize transfusion and hence decrease iron overload. However, another retrospective study demonstrated no survival benefit for MDS patients treated with ESAs.[48] The Eastern Cooperative Oncology Group conducted a prospective randomized trial comparing the efficacy and long-term safety of EPO with or without G-CSF plus supportive care versus supportive care alone for the treatment of anaemic patients with lower-risk MDS.[49] With a median follow up of 5.8 years, no differences were found in overall survival of patients in the EPO versus the supportive care arm or in the incidence of transformation to acute myeloid leukaemia. Response rates in this trial were 36% in the EPO-alone arm versus 9.6% in the supportive care arm. One patient developed a deep venous thrombosis in the EPO arm. Hence EPO can be effective in those patients with lower risk MDS, is considered safe and is not associated with an increased risk for mortality or leukaemic transformation.

Table 32.5 Predictive model for response to erythroid stimulating agent and G-CSF in myelodysplastic syndromes.

Variable	Probability of response (%)
Transfusions >2 units per month and serum erythropoietin >500 units l^{-1}	7
Only one of the above criteria	23
Neither criterion	74

Adapted from Hellstrom-Lindberg *et al.*[43]

Platelet growth factors have been an area of active research and investigation. Thrombopoietin is the endogenous hormone responsible for maintaining normal platelet counts. A pegylated derivative, megakaryocyte growth and development factor (MGDF), has been tested as an adjunct to supportive care in patients with AML induction therapy.[50,51] Its use did not decrease bleeding complications or reduce platelet transfusions in AML. Furthermore, when tested in healthy volunteers, it resulted in antiplatelet antibodies and thrombocytopenia, halting further development of this compound. Low doses of recombinant human interleukin-11, a thrombopoietic cytokine, have been tested in patients with MDS and bone marrow failure.[52] Five of 11 evaluable patients with MDS had an increase of platelet counts with a median duration of 12–30 weeks. Side effects even at low doses included fluid retention, peripheral oedema, conjunctival injection and myalgias. Romiplostin, a peptibody found to increase platelet production through the thrombopoietin (TPO) receptor c-Mpl, has been tested in clinical studies involving healthy volunteers and patients with chronic immune thrombocytopenia and found to increase the platelet count.[53] In a phase 1 study using this agent as part of supportive care in patients

with lower risk MDS, with baseline platelet counts of $\leq 50 \times 10^9 l^{-1}$,[54] durable platelet responses were achieved in 19 of 44 patients (46%). Bleeding events and platelet transfusions were reduced in those patients who had sustained responses. One thrombotic event was noted and reticulin grade in the marrow was increased in seven patients, unchanged in 10 patients and decreased in seven patients. No neutralizing antibodies to either romiplostim or endogenous TPO were found. Of concern was that two patients progressed to AML in the study and four cases of transiently increased blast counts were noted. No changes in cytogenetics were noted for patients with baseline and end-of-study cytogenetics available. Romiplostim has been tested in patients with low- or intermediate-risk MDS receiving azacitidine therapy, as an adjunct to supportive care.[55] There was no statistically significant difference seen in the groups receiving romiplostim 500 or 750 μg or placebo in terms of clinically significant thrombocytopenic events or platelet transfusions. However, romiplostim 750 μg significantly raised the median platelet count during cycle 3 on day 1 and at the nadir compared with the placebo.

Eltrombopag is an oral small-molecule non-peptide agonist of the thrombopoietin receptor. In a phase 1 placebo-controlled clinical trial of 73 healthy male subjects, eltrombopag given once daily in doses ranging from 5 to 75 mg resulted in a dose-dependent increase in the platelet count. There were no adverse events in the subjects receiving drug or placebo.[56] It is currently being studied in patients with high-risk MDS.

Pyridoxine, androgens, vitamins

The rationale for the use of pyridoxine in MDS is the potential improvement in ineffective erythropoiesis. Pyridoxine is a non-toxic cofactor required for haem biosynthesis and is usually given for 3 months in patients with anaemia from MDS, but responses are rare. There is no clear role for androgens, danzaol or vitamins in the therapy of MDS.

Immunosuppressive therapy

In the past, it was not uncommon to treat MDS patients with corticosteroids. Given the immunosuppression associated with the steroids, their routine use is not recommended although they may result in transient improvement in cytopenias. There is evidence that patients with hypocellular bone marrows (i.e. hypocellular MDS) have an immune or T-cell-mediated process.[57–59] In these patients, treatment with equine or rabbit antithymocyte globulin, a treatment commonly used for aplastic anaemia, has been found to be effective with response rates of >50%.[60] It is worth mentioning that a randomized trial comparing equine with rabbit antithymocyte globulin in patients with severe aplastic anaemia demonstrated superior results in terms of response and toxicity for the equine-treated arm.[61] Patients who typically respond are young and have low platelet counts and HLA-DR 15 histocompatibility antigen.[62] Although originally it was thought that only those with hypoplastic MDS would respond, it now seems clear that bone marrow hypoplasia is not a requirement for response.[63]

The success of immunosuppressive therapy in MDS is offset in part by the toxicities that can be associated with the antithymocyte globulin and the prolonged administration of ciclosporin. An alternative immunosuppressive regimen using the anti-CD52 antibody alemtuzumab was tested in patients with MDS who were judged likely to respond to immunosuppressive therapy based on HLA-DR status and time of red blood cell transfusion dependence.[64] In this small study, alemtuzumab 10 mg per day was administered intravenously over 10 days and response rates of 77% (17/22) in intermediate-1 patients and 57% (4/7) in intermediate-2 patients were observed with a median time to response of 3 months. At 12 months, five of nine patients who responded had normal blood counts and seven of nine patients were transfusion independent. Infections were the primary complications with 23% of participants reactivating cytomegalovirus and 68% reactivating Epstein–Barr virus. This study suggests that alemtuzumab may be a viable treatment for MDS patients judged likely to respond to immunosuppressive therapy.

Hypomethylating agents

Azacitidine (5-azacytidine, 5-aza, Vidaza) is a pyrimidine nucleoside analogue of cytidine, whose mechanism of action is thought to be DNA hypomethylation in addition to a direct cytotoxic effect on the haematopoietic elements of the bone marrow. A phase 3 clinical trial comparing azacitidine with best supportive care in 191 patients with MDS demonstrated a 60% response rate in those patients who received azacitidine 75 mg m^{-2} subcutaneously for 7 days every 28 days.[65] Importantly, only 7% were complete remissions; the other responses were partial remissions or haematological improvements. The benefit of azacitidine was seen in all risk groups of MDS patients. Complete and partial response rates were 23% versus 0% for the azacitidine and the supportive care arms, respectively. The median time to leukaemic transformation or death was 21 versus 13 months, respectively. In addition, there was a companion quality of life analysis that demonstrated azacitidine to be superior to supportive care.[66] Survival could not be adequately looked at because of the crossover design. Nonetheless, this regimen is well tolerated and can be administered on an outpatient basis. Major side effects include nausea and vomiting and also myelosuppression.

A large European study then compared azacitidine with conventional care in a phase 3 randomized trial in higher risk patients with MDS.[67] Conventional care consisted of

best supportive care, low-dose cytarabine or intensive or AML-type induction chemotherapy, as selected by participating investigators prior to randomization. The patients assigned to the intensive chemotherapy arm were more likely to be younger than 65 years, to have high-risk disease and to have AML by WHO criteria. Azacitidine treatment was continued in the absence of progression or unacceptable toxicity and the median number of cycles administered was nine. In this pivotal study, complete and partial remission rates for the azacitidine arm were superior to conventional care, at 29% versus 21%, respectively. With a median follow-up of 21.1 months, the median overall survival was 24.5 months for the azacitidine arm compared with 15 months for the conventional care arm ($p = 0.0001$). The favourable results with azacitidine seen in this trial compared with conventional care and prior azacitidine trials may be due in part to the long duration of therapy (median duration of therapy of >9 months) and to the appropriate selection of patients in the higher risk MDS category.

Another hypomethylating agent, decitabine (5-aza−2′-deocytidine), has also demonstrated promise as an agent for MDS. Chemically it is closely related to azacitidine. A phase 2 trial performed in Europe[68] demonstrated that decitabine has significant activity in MDS. In this multicentre trial of 66 patients with MDS, decitabine was given at 15 mg m^{-2} i.v. over 4 h every 8 h on days 1, 2 and 3, with cycles repeating every 6 weeks. With this schedule, the overall response rate was 25, 48 and 64% for those in the intermediate-1-, intermediate-2- and high-risk groups, respectively. The median survival time from the start of treatment for the high-risk patients was 1.2 years, compared with an expected survival of 0.5 years. In addition, 31% of patients with abnormal pretreatment cytogenetics had major cytogenetic responses. Toxicity associated with this drug includes fever, infection, sepsis, neutropenia, anaemia and thrombocytopenia. A phase 3 multicentre trial randomized 170 patients with MDS to decitabine 15 mg m^{-2} every 8 h for a nine doses every 6 weeks or supportive care with transfusions, antibiotics and growth factors.[69] The overall response rate in the decitabine arm was 17%, with 9% complete remissions, 8% partial responses and 13% haematological improvements. There was a significant trend towards delay in progression to AML or death in patients with intermediate-2- or high-risk disease, but disappointingly there was no survival benefit to decitabine in this trial.

A phase 3 study in higher risk MDS patients was conducted in Europe, which compared 119 patients treated with decitabine at 15 mg m^{-2} every 8 h for nine doses with 114 patients treated with best supportive care.[70] The response rate was 34% (13% complete response, 6% partial response and 15% haematological improvement). Again, no difference in overall survival or time to progression to AML was seen in the decitabine arm. Azacitadine and decitabine are chemically similar compounds with similar biological activity. The difference in survival benefit seen with one drug versus the other may be attributed to an inadequate number of cycles of decitabine being administered. In the European trial, a median of only four cycles of decitabine were administered compared with nine cycles in the European azacitidine trial for high-risk MDS patients.

In an attempt to decrease the toxicity associated with this agent, an alternative schedule for prolonged exposure has been explored and had a demonstrated efficacy of 65% in patients with haematological malignancies in a phase 2 trial.[71] Using a Bayesian design, patients were randomized among the following doses and schedules: 20 mg m^{-2} i.v. for 5 days, 20 mg m^{-2} subcutaneously for 5 days and 10 mg m^{-2} i.v. for 10 days. Decitabine 20 mg m^{-2} i.v. for 5 days was found to be the optimal dose and schedule with a complete remission rate of 39%. This is not the registration dose of the drug but represents a dose and schedule that are easily administered in the outpatient setting. The ADOPT trial confirmed the efficacy of this dose and schedule of decitabine for patients with MDS with an IPSS score of ≥ 0.5.[72] In this large, multicentre trial, 99 patients were enrolled. The overall response rate was 32% with 17 complete responses plus 15 marrow complete responses and a 51% overall improvement.

At this time, azacitidine and decitabine are approved for the treatment of patients with MDS. Azacitadine improves the survival of higher risk patients. In general, both agents should be given for 4–6 cycles before the treatment is considered a failure. Failure of response would be lack of any sort of response, including haematological improvement, complete response or partial response, progression to AML or toxicity that precludes further treatment. These agents are recommended for patients who are not candidates for high-intensity therapy, and also for patients as a 'bridge' prior to allogeneic stem cell transplant.

Lenalidomide

Lenalidomide, a thalidomide analogue, is approved by the FDA for the treatment of transfusion-dependent, low- and intermediate-1-risk MDS with a del(5q). In a multicentre phase 2 study,[73] 148 patients were treated with lenalidomide 10 mg daily for 21 days of a 28 day cycle (46 patients) or 10 mg daily every day (102 patients). Importantly, patients had the del(5q) alone or with other abnormalities, were transfusion dependent and had an absolute neutrophil count >500 μl^{-1} and a platelet count >50 000 μl^{-1}. At 24 weeks, 112/148[74] had a response; 99 patients (67%) became transfusion independent and another 13 patients had a reduction in their transfusion burden by 50%; 85 patients had adequate cytogenetic results at time of entry and at 24 weeks and a 45% complete cytogenetic response rate

was noted. Importantly, grade 3 and 4 neutropenia and thrombocytopenia were the most frequent toxicities seen and monitoring of blood counts weekly during the first 8 weeks or so of treatment is recommended. The median duration of response is ~2 years. Resistance has been seen and typically the re-emergence of the del(5q) clone is seen in conjunction with recurrent anaemia and or transfusion dependence. Features predicting response include age, shorter duration of disease, lower transfusion burden and treatment-related thrombocytopenia.

Lenalidomide activity has been seen in non-del(5q) MDS patients. A multicentre phase 2 study evaluated lenalidomide in transfusion-independent low- or intermediate-1-risk MDS patients without del(5q).[75] Again, eligible patients had to have adequate peripheral blood counts defined as an absolute neutrophil count $>500\,\mu l^{-1}$ and a platelet count $>50\,000\,\mu l^{-1}$ and had to have documented transfusion dependence. A total of 214 patients were treated with 10 mg of lenalidomide daily or 10 mg for 21 days of a 28 day cycle. Again, the most common grade 3 and 4 toxicities were neutropenia (30%) and thrombocytopenia (25%). A total of 56/114 patients (26%) achieved transfusion independence after a median duration of 4.8 weeks of treatment with a median duration of response of 41 weeks.

Lenalidomide has been tested in higher risk MDS patients with del(5q).[74] In a phase 2 study of 47 patients with intermediate-2- or high-risk MDS with a del(5q), lenalidomide 10 mg was administered for 21 days of a 28 day cycle. Thirteen patients (28%) had a response, including seven patients (15%) with a complete remission. Those patients who had a complete remission tended to have higher platelet counts at baseline and a del(5q) alone or with one other abnormality.

Interestingly, none of the phase 2 studies have demonstrated a survival benefit for lenalidomide in MDS patients. Because of reports of leukaemic transformation in patients with low-risk MDS being treated with lenalidomide, the European Medicines Agency (EMEA) did not approve the drug in Europe, pending more data on safety and the rate of leukaemic transformation.

Intensive therapy

Induction chemotherapy

For the most part, intensive and aggressive antileukaemic chemotherapy as is used for acute myelogenous leukaemia has not been as effective when used in patients with MDS. In a retrospective study from the University of Texas M.D. Anderson Cancer Center, outcomes with AML induction regimens were compared among those treated for AML, RAEB and RAEB-t.[76] This study demonstrated that patients with MDS (RAEB or RAEB-t) did equally as poorly or as well as those with AML after controlling for age and cytogenetics.[76] No data are available regarding the benefit of post-remission consolidation with high-dose ara-C in these patients, as older adults with AML do not benefit from this intensive approach as do younger adults with *de novo* AML.[77,78] The lack of benefit for intensive chemotherapy in these patients is due to a decreased capacity to tolerate intensive chemotherapy. Furthermore, the stem cell defect in MDS occurs in a very early or proximal stem cell, which is more likely to be resistant to chemotherapy due to the overexpression of the multi-drug resistant P-glycoprotein (MDR-1). This protein acts to confer resistance to chemotherapy. Several studies using modulators of MDR-1 plus standard induction regiments for AML have been performed on in patients with advanced MDS or AML from MDS in order to circumvent this mode of resistance. In one study, quinine was used as an MDR modulator in combination with mitoxantrone and cytarabine which resulted in a 52% complete response rate in those patients who expressed the P-glycoprotein compared with 18% for those patients who did not receive the quinine.[79] In another study using PSC833, no difference was seen in remission rates or overall survival between those who did and did not receive the MDR modulator.[80]

Haematopoietic stem cell transplantation

Because the defect in MDS occurs in an early haematopoietic precursor, allogeneic transplant represents a potentially curative option. Many studies have suggested that low-risk MDS patients and also those with high-risk disease experience a long-term disease-free survival from a matched related donor allogeneic transplant.[81–83] Unfortunately, many patients do not have this option of treatment either because of age, comorbidity or lack of a sibling donor. The use of non-myeloblative or reduced-intensity conditioning in older patients is growing. This treatment modality seeks to maximize the immune effect of graft versus leukaemia while minimizing the toxicity associated with ablative conditioning regimens. Non-myeloablative transplantation has a low short-term mortality rate in patients with MDS up to age 70–75 years with overall survival rates comparable to those for ablative transplantation, mainly due to the higher risk of relapse seen.[84] In a large retrospective series of 1333 MDS patients aged >50 years who received a transplantation within the European Group for Blood and Marrow Transplantation (EBMT), 449 (34%) were >50 years of age.[85] Overall survival for the entire cohort was 31% with a 4 year estimate of non-relapse mortality of 36% for all patients. For those >60 years of age, the overall survival was 27% and the non-relapse mortality was 36%. In another study examining the effect of age on the outcome of reduced-intensity haematopoietic cell transplantation in older patients with AML or with MDS, age was not found to have a significant impact on non-relapse mortality, relapse, disease-free survival or overall survival.[86] In

this series, HLA mismatch, unfavourable cytogenetics and pre-stem cell transplant performance status were predictors for improved 2 year overall survival.

Key points

- Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by dysplasia, ineffective haematopoiesis and potential risk of transformation into acute leukaemia.
- In MDS, the important predictors for overall prognoses are cytogenetic abnormalities, percentage of myeloblasts in the bone marrow and the number of lineages that exhibit cytopenias.
- Because the defect in MDS occurs in an early haematopoietic precursor, allogeneic transplant represents a potentially curative option.

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CHAPTER 33

Management of myelodysplastic syndromes and acute leukaemia

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Introduction

Myelodysplastic syndromes (MDS) encompass a heterogeneous group of disorders characterized by ineffective haematopoiesis typically resulting in cytopenias. MDS is clearly a disease of ageing patients and will be commonly encountered in primary care and geriatric practices. MDS may behave as an indolent disease or progress to bone marrow failure or acute leukaemia. Acute leukaemias are clonal disorders characterized by a proliferation of immature myeloid [acute myeloid leukaemia (AML)] or lymphoid [acute lymphocytic leukaemia (ALL)] cells. Accumulation of leukaemic cells impairs the normal haematopoietic function of the bone marrow, resulting in cytopenias with or without leukocytosis. While relatively uncommon, the incidence of acute leukaemias, particularly AML, increases with age. In addition, management issues are increasingly complex in older adults due to the aggressive nature of both the disease and the treatments required for cure. This chapter outlines key diagnosis and management issues for older adults with MDS and acute leukaemias.

Myelodysplastic syndromes

The myelodysplastic syndromes (MDS) represent a broad group of clonal haematopoietic disorders characterized by ineffective haematopoiesis resulting in peripheral blood cytopenias. In these diseases, cells of the affected lineage are unable to undergo maturation and differentiation, resulting in cytopenias. The major clinical significance is the morbidity associated with profound cytopenias and the potential to evolve into AML.

MDS are clearly diseases of ageing patients, with a median age at diagnosis of 76 years.[1] It is estimated that over 80% of the 10–15 000 patients diagnosed in 2010 will be over age 60 years.[2] Unfortunately, survival for MDS has been poor with a reported three-year overall survival rate of 35%.[3] Complications of bone marrow failure are a leading cause of death for these patients. The incidence of these disorders is likely to rise with the ageing of the US population making this an increasingly important public health concern.

Advanced age is the primary risk factor for developing MDS. Most patients diagnosed with MDS have no other known predisposing risks. Exposures that have been associated with subsequent development of MDS include chemotherapy, radiation, agricultural chemicals (i.e. pesticides), solvents and tobacco smoking. Of these, exposure to alkylating agent chemotherapy (i.e. melphalan) has been most well defined. Alkylating agent associated MDS typically presents within five to seven years after exposure and is characterized by abnormalities in chromosomes 5 and 7.

Diagnosis and prognosis

Diagnosis of MDS relies primarily on peripheral blood and bone marrow findings. The diagnosis should be suspected in individuals presenting with persistent cytopenia. Careful attention should be paid to consistent decreases in blood counts over time in an older adult which may signify early developing MDS. A frequent presentation can be progressive macrocytic anaemia in an older adult. Many patients are asymptomatic at the time of diagnosis. However, careful history-taking should include questions regarding recurrent infections, bruising, bleeding, duration of cytopenia and need for red cell transfusion. The differential diagnosis for suspected MDS includes megaloblastic anaemia (B12 and folate deficiency), AML, aplastic anaemia, copper deficiency, viral infections (HIV), large granular lymphocytic leukaemia, paroxysmal nocturnal haemoglobinuria (PNH), and heavy metal poisoning.

The initial workup includes a CBC with differential, reticulocyte count, RBC folate, serum B12, iron studies and review of the peripheral smear. Classic peripheral blood

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findings associated with MDS include macrocytosis and hypogranular, hypolobated neutrophils (pseudo-Pelger-Huet anomaly). A bone marrow biopsy with cytogenetic analysis is necessary to confirm the diagnosis. The bone marrow is typically hypercellular with dysplastic features. The percentage of myeloblasts in the marrow helps differentiate between an MDS and AML. Cytogenetic abnormalities play an increasingly important role in the diagnosis and prognosis of MDS. Clonal chromosomal abnormalities can be detected in approximately 50% of patients with MDS.[4] Diagnosis of certain MDS subtypes (such as the 5q minus syndrome) is entirely dependent upon detection of specific cytogenetic abnormalities. Cytogenetic testing, therefore, should be performed as part of bone marrow evaluation in all patients with suspected MDS to inform the diagnostic workup, prognosis and treatment options.

The classification of MDS has evolved. Historically, the French-American-British (FAB) Cooperative Group classification system was used which included five diagnostic categories based on peripheral blood and bone marrow characteristics. Categories included refractory anaemia (RA), RA with ring sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEBT), and chronic myelomonocytic leukaemia (CMML). A more recent classification scheme was proposed and updated by the World Health Organization (WHO) which incorporates cytogenetic abnormalities.[5] This classification scheme is presented in Table 33.1 and reflects the heterogeneity of MDS.

The natural history of patients with MDS syndromes is quite variable. It is well established that mutagen-induced MDS is associated with a poor prognosis and that increased age is also a negative prognostic factor. However, the

Table 33.1 WHO Classification of peripheral blood and bone marrow findings in myelodysplastic syndromes.

Disease	Blood findings	Bone marrow findings
Refractory cytopenias with unilineage dysplasia (RCUD)	Unicytopenia or bicytopenia	Dysplasia in ≤10% of cells in one myeloid lineage
Refractory anaemia Refractory neutropenia Refractory thrombocytopenia	No or rare blasts	<5% blasts <15% ringed sideroblasts
Refractory anaemia with ringed sideroblasts (RARS)	Anaemia No blasts	≥15% ringed sideroblasts Erythroid dysplasia only <5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias No or rare blasts (<1%) No Auer rods $1 \times 10^9\ l^{-1}$ monocytes	Dysplasia in ≥10% of the cells of two or more myeloid cell lines <5% blasts in marrow No Auer rods ±15% ringed sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenias <5% blasts No Auer rods $1 \times 10^9\ l^{-1}$ monocytes	Unilineage or multilineage dysplasia 5–9% blasts No Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenias 5–19% blasts Auer rods ± $1 \times 10^9\ l^{-1}$ monocytes	Unilineage or multilineage dysplasia 10–19% blasts Auer rods ±
Myelodysplastic syndrome-unclassified (MDS-U)	Cytopenias ≤1% blasts	Dysplasia <10% of cells in one or more myeloid cell lines accompanied by a cytogenetic abnormality that is characteristic for MDS <5% blasts
MDS associated with isolated del (5q)	Anaemia Usually normal or increased platelet count <1% blasts	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

Adapted from Brunning R *et al. Tumours of Haematopoietic and Lymphoid Tissues*. Geneva: World Health Organization, 2008.

Table 33.2 International Prognostic Scoring System (IPPS) for MDS.

(a) IPSS Scoring System	**0**	**0.5**	**1.0**	**1.5**
Bone marrow blasts (%)	<5	5–10	–	11–20
Karyotype[a]	Good	Intermediate	Poor	–
Cytopenias	0/1	2/3	–	–

(b) IPPS Risk Category	Overall score	Median survival (years)
Low	0	5.7
Intermediate-1	0.5–1.0	3.5
Intermediate-2	1.5–2.0	1.2
High	≥2.5	0.4

[a]Karyotype definitions: Good risk = normal, -Y, del(5q), del (20q); Poor risk = ≥3 abnormalities, abnormal chromosome 7; Intermediate risk = all other abnormalities.
Adapted from Greenberg *et al.*[6]

heterogeneity of this disease has complicated accurate prognostication in *de novo* MDS. The International Prognostic Scoring System (IPSS) (Table 33.2(a)) was developed to risk stratify patients at the time of diagnosis based on cytogenetic, morphological and clinical data. The IPSS for MDS was developed based on an analysis of 816 patients which demonstrated that specific cytogenetic abnormalities, the percentage of blasts in the bone marrow, and the number of haematopoietic lineages involved in the cytopenia were the most important variables in disease outcome.[6] Risk scores are determined based on these variables, and a categorization of low risk, intermediate-1, intermediate-2, and high risk is assigned (Table 33.2(b)). The IPSS demonstrated improved prognostic discrimination over earlier classification schemes and has been incorporated into clinical practice and subsequent trial design.

There are multiple known prognostic factors that are not included in the IPSS classification. For example, chronological age is not incorporated into the IPSS score. The prognostic impact of increasing age, however, differs by IPSS risk group. In the original analysis used to develop the IPSS, survival for high-risk patients appeared to be independent of age. This suggests survival was driven primarily by tumour biology in these patients.[6] Survival for low-risk patients was strongly dependent on age with median survival of 9.0 years versus 3.9 years for age groups <70 and ≥70 years respectively. Therefore additional factors such as comorbid disease may influence survival in the setting of more indolent MDS.

The IPSS classification system has several limitations: (1) it does not account for duration of disease; (2) subjects who received prior therapy or had secondary MDS were excluded; and (3) it does not account for performance status or comorbid disease. Additional classification schemes have been proposed which include prognostic factors such as poor performance status, older age, prior transfusions and time elapsed from diagnosis.[7] Despite its limitations, the IPSS classification remains a useful tool in clinical practice.

Treatment

Treatment strategies for MDS have been evolving in recent years to target higher risk MDS and subgroups defined by specific cytogenetic abnormalities. Treatment goals include managing cytopenias, decreasing progression to AML, improving overall survival while maintaining quality of life. Current treatment recommendations for MDS involve a risk-adapted therapeutic approach. In general, the National Comprehensive Cancer Center (NCCN) guidelines recommend classifying patients into relatively low risk (IPSS Low or Intermediate-1 categories) and higher risk (IPSS Intermediate-2 and High categories).[8] Supportive care aimed at controlling symptoms related to cytopenias is the mainstay of treatment for: (1) low-risk patients and (2) patients with poor functional status or limiting comorbid conditions regardless of IPSS classification. Higher risk patients with good functional status and manageable comorbid conditions should be considered for low-intensity chemotherapy along with best supportive care.

Supportive care typically constitutes red cell and platelet transfusions, antibiotics for infection, haematopoietic growth factors such as recombinant erythropoietin (epoetin alpha) for selected patients, and iron chelation. Patients with symptomatic anaemia, or transfusion-dependent anaemia, may benefit from epoetin alpha or a longer acting form darbepoetin alpha. Response rates in studies are approximately 50% (major response is defined by haemoglobin increase $>2\,g\,dl^{-1}$ or transfusion independence, minor response is defined by haemoglobin increase $1–2\,g\,dl^{-1}$ or 50% reduction for transfusion-dependent patients).[9] Patients most likely to respond to use of erythropoietin are those with IPSS score low/intermediate-1, serum erythropoietin level <500, and transfusion requirement of <2 units of red cells per month.[10] The NCCN recommends a target haemoglobin of $\leq 12\,g\,dl^{-1}$. Granulocyte colony stimulating factor (G-CSF) may have a synergistic effect in combination with epoetin for treatment of anaemia. Low dose G-CSF dosed three times per week can be added to erythropoietin if response is inadequate to epoetin alone. Use of growth factors for symptomatic anaemia has been associated with improved quality of life and decreased transfusion requirement without increased risk of progression to AML.[8,11] However, no improvement in survival has been attributed to this intervention. Responses in haemoglobin levels are typically evident within 6–8 weeks of treatment.

Ongoing treatment is not indicated if no response is detected during this time period.

Over time, most patients become transfusion dependent, increasing the risk of iron overload. Secondary iron overload negatively affects survival in transfusion-dependent patients.[12] Current consensus guidelines recommend iron chelation therapy for those patients most likely to suffer negative consequences from chronic iron overload.[8] The patients most likely to benefit from chelation are those with lower risk MDS, ongoing transfusion dependence, and anticipated survival of greater than one year. For these patients, initiation of iron chelation therapy should be considered after transfusion of 20–30 units of red cells or the serum ferritin exceeds $2500\,\mu g\,l^{-1}$. Serum ferritin can be used to monitor efficacy of chelation with goal ferritin $<1000\,\mu g\,l^{-1}$ on treatment. Chelation agents include deferoxamine or the oral agent deferasirox.

Patients in the higher risk IPSS categories are more likely to experience morbidity related to cytopenias and to progress to acute leukaemia in a shorter time interval from diagnosis. For patients who present with high-risk disease or show evidence of progression to high-risk disease during follow-up, treatment with low-intensity chemotherapy should be considered. The low-intensity chemotherapeutic agents which have demonstrated efficacy in treatment of MDS are the hypomethylating agents 5-azacytidine and decitabine.

The first chemotherapy agent to demonstrate efficacy in treatment of MDS was 5-azacytidine. A randomized controlled trial of 191 patients which compared treatment with 5-azacytidine to supportive care alone for high-risk MDS demonstrated significant improvements in response, time to AML progression, and survival.[13] Eligible patients (median age 68) met FAB classification criteria for MDS and were considered high risk. The 5-azacytidine was administered at a dose of $75\,mg\,m^{-2}$ for 7 consecutive days on a 28-day cycle. The response rate (complete and partial) was 23% in the treatment arm with median time to leukaemic progression 21 versus 13 months for supportive care ($p = 0.007$). After controlling for the effect of crossover from placebo to active treatment, there was a survival advantage detected in treated patients.

Importantly, this study also evaluated quality of life outcomes.[14] Treatment with 5-azacytidine was associated with significant improvement in fatigue, dyspnoea, self-reported physical functioning and psychological distress. Quality of life differences were maintained after controlling for the number of transfusions received. The improvements in both disease-related outcomes and quality of life established the use of 5-azacytidine as a standard of care for treatment of high-risk MDS. Another randomized controlled international trial of 358 patients confirmed an overall survival benefit favouring 5-azacytidine over physician-directed conventional care.[15]

Based on treatment experience from these randomized studies it is generally recommended to treat for approximately 4–6 cycles if tolerated to determine response for individual patients. Treatment protocols typically recommend treating for an additional three cycles after achieving complete remission or for as long as a treatment benefits persist in patients with a lesser response.

Decitabine, a second pyrimidine nucleoside analogue of cytidine which inhibits DNA methylation, is also FDA approved for the treatment of higher risk MDS. A randomized study of 170 patients (median age 70) compared decitabine versus supportive care for patients who met FAB classification for MDS and had an IPSS score ≥ 0.5.[16] The dose schedule was $15\,mg\,m^{-2}$ given intravenously every 8 hours for 3 days on a 6-week cycle. Patients treated with decitabine had a 17% overall response rate with an additional 13% demonstrating haematological improvement. Patients with intermediate-2 or high-risk disease by IPSS classification demonstrated improvement in progression to AML (12 months versus 6.8 months). In this study the median number of treatment cycles administered was three with responding patients receiving a median of six cycles (range 2–8). Temporary dose reduction or delay was required in 35% of patients on treatment. Evaluation of quality of life demonstrated improvements in global health status, fatigue, and dyspnoea favouring active treatment.

A follow-up randomized study evaluated different treatment dosing schedules of decitabine.[17] A five-day intravenous schedule which had the highest dose intensity was determined to be optimal. This dosing schedule is convenient for outpatient treatment and has become an acceptable option in clinical practice. At the present time there is no randomized clinical trial data that compares decitabine directly to 5-azacytidine. These agents are generally considered to be similar in efficacy although documentation of overall survival benefit favours 5-azacytidine. Current evidence would suggest that the patients most likely to benefit from these agents are those with intermediate-2 or high-risk classification by IPSS.

While these medications are associated with toxicity, they represent the mainstay of treatment for older adults with higher risk MDS who have a good performance status. The primary toxicity seen is myelosuppression. Often cytopenias will worsen in the first few months of treatment prior to demonstrating evidence of response. Consequences of myelosuppression can be managed in older adults with temporary increased use of transfusion support, growth factor support and prophylactic antibiotics for neutropenia. Higher intensity therapy such as allogeneic transplantation, to date the only curative therapy for MDS, is generally restricted to younger adults with acceptable donors due to the high morbidity and mortality associated with the therapy itself.

Treatment options have expanded for patients with MDS associated with chromosome 5q deletion. The 5q- syndrome is a specific MDS subset defined by deletion of the long arm of chromosome 5 as the sole abnormality without excess bone marrow blasts. The 5q- syndrome typically manifests as refractory anaemia, often with normal or even increased platelet counts, and is considered a more favourable MDS subset because a large percentage of patients do not progress to acute leukaemia. Lenalidomide, an oral immunomodulatory drug, has demonstrated efficacy in this setting. In a phase 2 clinical trial of 148 patients, significant decrease in transfusion requirements and reversal of cytogenetic abnormalities was demonstrated.[18] Eligible patients met FAB criteria for MDS, had a chromosome 5q31 deletion that was either in isolation or combined with additional cytogenetic abnormalities, low or intermediate-1 IPSS score, and transfusion-dependent anaemia. The majority of patients (64%) had isolated 5q deletion. Lenalidomide was dosed 10 mg daily orally for 21 days of a four-week cycle. Transfusion independence was achieved in 67% of participants. Median time to response was rapid at 4.6 weeks. The primary toxicity in this study was myelosuppression with neutropenia and thrombocytopenia. This typically occurred within the first eight weeks of treatment. Dose adjustment was required in the majority (84%) of patients. This drug has become the standard of care for treatment of transfusion-dependent, lower risk patients with chromosome 5q deletion and reinforces the clinical and therapeutic importance of cytogenetic evaluation in MDS.

Despite recent advances in pharmacological treatment options, there are unresolved clinical questions related to the treatment of older adults with MDS. One major issue is patient selection. Clinical trials in MDS have included a substantial number of older adults. However, most studies included only patients with good functional status.[13,16] Many older adults with MDS in clinical practice present with functional impairments. It is unclear if the beneficial results seen in clinical trials can be extrapolated to older adults with impaired performance status. This results in a substantial proportion of older adults for whom there is no evidence-based treatment recommendation.

Clinical experience suggests that some older adults with poor performance status may benefit from low-intensity chemotherapy, particularly those whose functional decline was related to disease progression. Alternatively, some older adults with impaired functional status may experience increased morbidity with active treatment. The interaction between presence of specific comorbidities and treatment benefit has also been understudied. Clinical trials targeting older adults with impaired performance status are needed which emphasize both disease-specific outcomes and quality of life.

Another issue for treatment of MDS in older adults is the balance between ongoing maintenance therapy for disease control and quality of life. It is unclear how long older adults who respond to hypomethylating agents should remain on treatment. Studies would suggest continuing treatment until intolerance or progression. Over time, many older adults can develop toxicities and functional decline due to ongoing therapy. The impact of continuous treatment versus sequential treatment strategies on disease control and quality of life is unknown.

There are multiple new therapeutic approaches for MDS under investigation. There is an increasing focus on development of targeted therapies that is informed by improved understanding of biological mechanisms underlying the MDS syndromes. Future treatment algorithms will likely differentiate specific disease subtypes such as the 5q- syndrome which are susceptible to targeted therapeutic approaches. Combining novel agents with hypomethylating agents to improve efficacy is another investigational approach. Finally, improved patient-assessment strategies will help identify which older patients with high-risk MDS may benefit from more aggressive treatment approaches such as reduced-intensity allogeneic transplantation.

Acute myelogenous leukaemia (AML)

AML is a disease of older adults, with a median age at diagnosis of 67 years.[2] The American Cancer Society estimated that 12 330 patients would be diagnosed with AML in 2010 with an anticipated 8950 dying of the disease.[2] The incidence of AML increases dramatically with age (Figure 33.1) and there is a persistent age-related survival disparity (Figure 33.2). Multiple factors contribute to poor treatment outcomes in older adults including aggressive tumour biology and poor tolerance to aggressive therapies due to functional limitations and comorbid conditions.

The primary risk factors for developing AML are increasing age and a history of prior MDS. Less common risk factors include exposure to certain chemotherapy drugs (alkylating agents, topoisomerase 2 inhibitors, and nitrosoureas), radiation or benzene exposure, and a history of Down syndrome.

Diagnosis and prognosis

The clinical signs and symptoms of AML can be varied and non-specific. However, in contrast to MDS, symptoms are typically acute in onset and often prompt medical evaluation. Common symptoms include fatigue, bleeding, fever and infection. Symptoms are typically related to cytopenias, often pancytopenia due to leukaemic infiltration of the marrow. Less commonly, older adults with AML may present with severe leukocytosis, which can produce symptoms of leukostasis due to the large peripherally circulating blast fraction. Leukostasis symptoms include altered mental status, shortness of breath, or chest pain. Occasionally patients

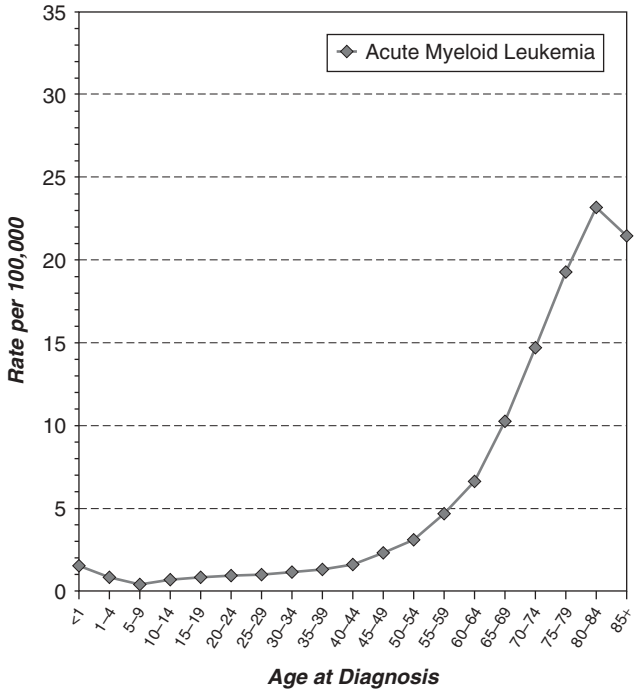

Figure 33.1 The incidence of AML as a function of age: 2000–2007 SEER (Surveillance Epidemiology and End Results) data. Source: http://seer.cancer.gov.

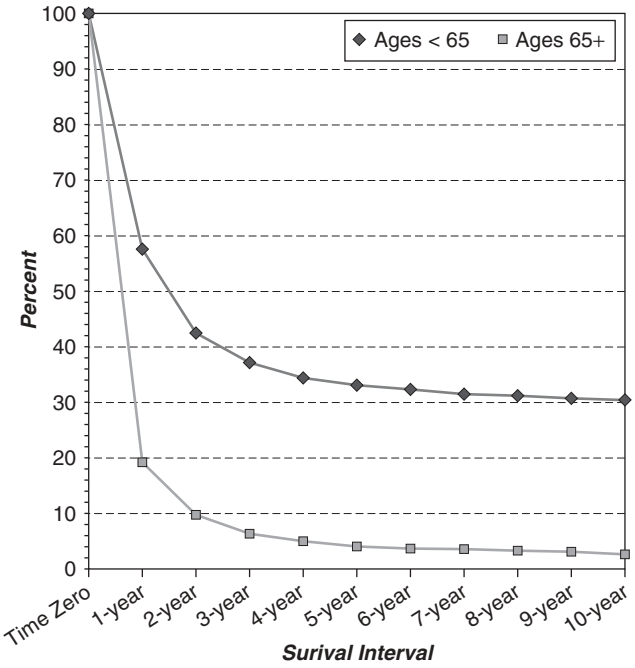

Figure 33.2 Relative survival by age group from Surveillance Epidemiology and End Results (SEER) data 1988–2006. Source: http://seer.cancer.gov.

may present with leukaemic infiltration of tissues outside the bone marrow such as the liver, spleen, lymph nodes, skin or central nervous system which can produce a variety of site-specific symptoms. Initial peripheral blood findings range from pancytopenia with or without circulating blasts cells to severe leukocytosis (primarily blasts) with accompanying anaemia and pancytopenia.

The diagnosis of AML is established by bone marrow biopsy when the percentage of leukaemic blasts of myeloid lineage is ≥20%.[19] Morphological evaluation can be aided by immunohistochemical and flow cytometry techniques to confirm myeloid versus lymphoid origin. For patients who present with leukocytosis, flow cytometry alone can establish the diagnosis. The historical international classification system (FAB) details subtypes of AML (M1 through M7) based on morphology, histochemical characteristics, and immunophenotyping. The more recently proposed WHO classification of AML (Table 33.3) highlights the importance of a cytogenetic classification for prognosis and treatment and has become the standard classification scheme. It has become increasingly clear in recent years that AML encompasses a group of distinct diseases with a broad range of tumour biology. Subsets of AML defined by specific cytogenetic abnormalities have been shown to be associated with improved prognosis such as the core binding factor leukaemias [inv(16), t(8;21), t(16;16)], and acute promyelocytic leukaemia (APL) [t(15;17)]. Treatment strategies targeting specific AML subtypes have been developed to maximize clinical outcomes and minimize toxicity based upon cytogenetic classification.

Table 33.3 WHO (2008) Classification of acute myeloid leukaemias and related precursor neoplasms.

Acute myeloid leukaemia with recurrent genetic abnormalities[a]
Acute myeloid leukaemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukaemia not otherwise specified (NOS)
Myeloid sarcoma
Myeloid proliferation related to Down syndrome
Blastoid plasmacytoid dendritic neoplasm

[a]Examples include core binding factor leukaemias[i.e. t(8;21), inv(16)], and acute promyelocytic leukaemia with t(15;17).
Adapted from Vardiman *et al.*[5]

If untreated or unresponsive to chemotherapy, AML may be rapidly fatal (median survival <2 months). The major causes of death are overwhelming infection and haemorrhage related to the disease-associated cytopenias. Survival for AML is age-dependent, with five-year survival rates as low as 5% among patients ≥65 years compared to approximately 30% for those <65.[2] This age-related outcome disparity is also seen in clinical trials. In addition, older adults are more likely to experience treatment-related toxicity. Due to concerns regarding inferior outcomes, a

large proportion of older adults in the United States are not referred for chemotherapy treatment of their disease.

Age-related changes in tumour biology are a major determinant of poor outcome in older adults with AML.[20,21] Older patients have a higher percentage of unfavourable cytogenetic abnormalities (i.e. chromosomes 5 and 7 abnormalities, and complex karyotypes) and a lower percentage of favourable cytogenetic abnormalities [i.e. t(8;21), and inv(16)] compared to younger patients. Unfavourable cytogenetic abnormalities are associated with decreased remission rates and shortened overall survival. Intrinsic drug resistance, mediated by the expression of a multidrug resistance phenotype (MDR1), is also more common in older AML patients. This provides an advantage to the leukaemia cells when treated with conventional agents such as anthracyclines. Finally, older adults are more likely to present with secondary AML arising in the setting of myelodysplastic syndrome (MDS), which is less responsive to standard therapies. While each of these poor prognostic features can individually influence remission rates, the combination of poor prognostic features is dramatically associated with lower remission rates with standard therapies. For example, older adults with the combination of *de novo* AML, MDR1 negative phenotype, and favourable/intermediate cytogenetics may have a complete remission (CR) rate as high as 81% compared to a CR rate of only 12% in those with MDR positive phenotype, secondary AML, and unfavourable cytogenetics.[22]

Despite the impact of tumour biology, striking differences in treatment outcomes persist between older and younger adults after stratifying for cytogenetic risk group.[20] Older adults with favourable cytogenetic profiles continue to experience inferior outcomes relative to younger patients with the same disease. Patient-specific factors, such as comorbidity and functional impairment, influence an older adult's ability to tolerate tumour burden and aggressive treatments. Increased comorbidity burden has been independently associated with lower remission rates, increased treatment-related mortality and poor overall survival. In one study, treatment-related death among older adults was 3% for patients who screened negative for comorbid conditions compared to 30% for those screening positive for majority comorbidity using a validated comorbidity index.[23]

Similarly, physical function at the time of diagnosis is strongly associated with prognosis. Older adults who present with poor performance on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (score >2, spending more than 50% of the day resting) are at increased risk for treatment-related mortality and poor survival. The prognostic importance of poor performance status increases significantly with chronological age. For example, clinical trial evidence suggests that the treatment-related mortality rate is approximately 30% for patients aged 56–65 years with poor performance status (ECOG score >2) compared to 80% for those >75 years of age with a poor performance status.[20]

Treatment

There is significant debate regarding optimal treatment for older adults with AML. While selected older adults can benefit from standard aggressive therapies, many experience increased morbidity and poor treatment response. Curative treatment for AML typically involves induction and consolidation chemotherapy. Initial (induction) chemotherapy is given in the hospital and is associated with long hospital stays (mean 20+ days) due to expected complications of myelosuppression including transfusion dependence and infections. The goal of this intensive chemotherapy is to produce marrow aplasia, followed in a few weeks by reconstitution of bone marrow. Remission requires recovery of peripheral blood counts and <5% myeloid marrow blasts. Post-remission chemotherapy (consolidation) is required for cure.

Standard induction therapy for AML is combination chemotherapy that includes cytosine arabinoside (Ara-C) and an anthracycline such as daunorubicin. A landmark randomized study by Löwenberg *et al*. demonstrated improved survival in selected patients ≥65 years of age treated with induction therapy versus supportive care alone.[24] In addition, there was no difference in time spent hospitalized between the two groups. This study paved the way for considering curative therapy options for older adults.

Unfortunately, many subsequent studies have failed to improve upon the suboptimal treatment outcomes seen in the older population. While complete remission rates range from 40–60%, median survival remains less than a year on clinical trials. Dose-attenuated treatments, designed to minimize toxicity, have not resulted in substantial improvement in outcomes. Haematopoietic growth factors including granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) have not consistently been shown to improve response rates or survival; likewise they do not clearly decrease costs. To date, no induction chemotherapy regimen tailored to the older adult population has clearly demonstrated improvement in clinical outcomes.

Optimal post-remission therapy for older adults also remains unclear. It is generally accepted that post-remission therapy or consolidation is required to eradicate residual leukaemia after induction. Typical post-remission treatment includes high-dose Ara-C or haematopoietic stem cell transplantation. In a randomized study of low-, intermediate- and high-dose Ara-C for consolidation in patients who had achieved complete remission, younger patients benefited from dose escalation

while older patients experienced more cerebellar toxicity and no benefit in disease-free survival.[25] In elderly specific trials, lower dose Ara-C regimens as a single agent or in combination with an anthracycline have been tested. In this population, there is no clear evidence to date that multiple courses of consolidation or maintenance therapy improve outcomes when compared to a single course of consolidation therapy.

Haematopoietic stem cell transplantation is another post-remission therapy option. In younger adults, high-dose chemotherapy followed by autologous stem cell transplantation can be considered for patients with intermediate-risk cytogenetics. Autologous haematopoietic stem cell transplantation is feasible in highly selected older adults with AML.[26] However, there is no randomized trial data to suggest superiority of this strategy over conventional chemotherapy and treatment-related mortality remains high (15–30%).

Allogeneic stem cell transplantation remains a standard post-remission treatment option with potential for long-term survival in younger adults with poor-risk cytogenetics. Traditional allogeneic haematopoietic cell transplantation (allo-HCT) is associated with very high treatment-related mortality in older adults and is therefore not recommended as post-remission therapy for most patients >60 years of age. Use of reduced-intensity allogeneic transplantation regimens ('non-myeloablative regimens') have resulted in a trend towards increased allogeneic transplantation in adults over age 50. This type of transplantation utilizes the graft versus leukaemia effect and reduces acute toxicities associated with use of myeloablative therapies. While this therapy may be feasible in highly selected older adults, it is yet unclear if this treatment strategy is superior to conventional approaches.

Post-remission therapy for older adults is further complicated by a higher likelihood that patients will no longer be candidates for additional treatment due to functional impairment or end organ damage resulting from induction therapy. In many cases a curative treatment approach must be aborted due to poor performance status that precludes post-remission treatment. In randomized trials, up to 20% of older adults may not go on to receive any consolidation therapy after achieving complete remission.[27] Attrition is much higher for older adults considered for post-remission transplantation.

Treatment recommendations differ for patients with acute promyelocytic leukaemia (APL). APL is characterized by a translocation between chromosomes 15 and 17 leading to the fusion of the promyelocytic leukaemia (*PML*) gene with the retinoic acid receptor α (*RAR*α) gene, resulting in disruption of normal cell differentiation.[28] While less common among older adults, this fulminant disease has a very high response and cure rate with current therapies that include use of all-*trans* retinoic acid (ATRA) which overcomes the differentiation block. A unique clinical feature of APL is presentation with bleeding secondary to disseminated intravascular coagulation and requires emergent treatment. Haemorrhage is a frequent cause of early mortality, particularly if untreated. When suspected, treatment with ATRA should begin immediately. Curative treatment includes induction with anthracycline and ATRA therapy followed by consolidation and maintenance therapy. The treatment course may span 1–2 years with remission rates ranging between 75–90%. In addition, relapsed patients may respond to arsenic trioxide, with a high proportion achieving a second remission. This subtype of AML should be treated aggressively in older adults given the high probability of response.

Regardless of AML subtype, supportive care is a key component of treatment for AML. Improvements in survival for AML over the past decades have been largely attributed to improved supportive care during induction. Older adults referred for AML therapy should be treated at high-volume centres with standard supportive care algorithms in place. Key components of supportive care include aggressive treatment of neutropenic fever (absolute neutrophil count <1000, temperature >100.5°F) and transfusion support. Patients with neutropenic fever should be started on broad spectrum intravenous antibiotics with gram negative coverage regardless of symptoms. Cultures are often negative but should be obtained routinely. Antibiotic regimens should be broadened to include antifungal coverage if fevers persist despite use of appropriate antibacterial therapy. Transfusion support is also a critical part of supportive care for patients with AML. During induction and consolidation therapy red cell transfusions are regularly required due to marrow hypoplasia. In addition, platelet transfusions are indicated for bleeding or prophylactically to prevent spontaneous intracranial bleeding using a threshold of $<10\,000\,\mu l^{-1}$.

In summary, treatment recommendations for older adults with AML need to be individualized based on tumour biology and an assessment of physiologic age rather than chronological age alone. While optimal therapy for older adults as a group remains debated, there is some evidence to guide decision-making for individual patients. Older adults with newly diagnosed AML who present with any of the following characteristics are more likely to experience toxicity and less likely to benefit from standard induction chemotherapy: an ECOG score >2, significant comorbidity (Charlson Comorbidity Index score >1), and poor-risk cytogenetics. It would be reasonable to offer these patients supportive care alone, low-intensity therapy or a clinical trial investigating novel agents. Alternatively, older adults with good functional status (ECOG <2, no impairment in IADLs), minimal comorbidity, and good-risk cytogenetics are likely to benefit from curative therapies. Optimal treatment for the large population of older adults who fall

between these two extremes is unclear. Prospective studies are needed to validate the added prognostic value of risk stratification based on factors other than chronological age and cytogenetic risk group.

Future directions

Investigation of novel agents to be used in addition or as a supplement to standard induction may improve outcomes for older adults with AML in the future. Development of less toxic more targeted agents may provide treatment alternatives for the large proportion of the elderly AML population who have less than optimal functional status, limiting comorbidities or unfavourable tumour biology. Clinical trials are in development that target treatments to specific biological subsets of AML in the elderly. In addition, clinical trials are also evaluating the use of geriatric assessment techniques to improve risk stratification among this patient population. Finally, supportive care strategies are being developed that focus attention on the maintenance of functional status and quality of life for those patients who are treated with aggressive therapies.

Acute lymphoblastic leukaemia (ALL)

Approximately 4000 cases of ALL are diagnosed yearly in the United States, with only one third of these cases in adults.[2] There is a bimodal incidence peak between ages 2 and 5 years, and again after age 50 years. With available therapy today, childhood ALL is curable in the majority of patients. ALL in adults is not the same as the childhood disease. First, the frequency of complete response is lower −70–75% in adults as opposed to more than 90% in children. Second, the remission duration and curability using the same therapy is considerably less.

ALL is broadly classified according to WHO criteria as follows: (1) precursor B-cell ALL; (2) precursor T-cell ALL; and (3) mature B-cell leukaemia (Burkitt leukaemia). Precursor B-cell ALL represents the majority of cases. Within these categories, several subgroups are identified based on cytogenetic abnormalities which have prognostic significance. These lymphoblastic neoplasms can present as either leukaemia or lymphoma. They are classified as leukaemia if there are >25% bone marrow blasts.

Common clinical manifestations at diagnosis include symptoms of pancytopenia (fatigue, bleeding, bruising, infection), and constitutional symptoms (fevers, night sweats, weight loss). Central nervous system involvement is common particularly in precursor B-cell ALL. In contrast to AML, hepatosplenomegaly and lymphadenopathy may be seen in up to half of adult patients. Precursor T-cell ALL, which is typically seen in younger patients, often presents with an anterior mediastinal mass. Diagnosis is made by bone marrow biopsy with morphologic and immunophenotypic analysis.

Important prognostic features for outcome in the treatment of ALL include older age, cytogenetics, and immunophenotype. Poor prognosis is especially associated with the presence of chromosomal translocations such as Philadelphia (Ph+) chromosome t(9;22), t(4,11), t(8;14), t(2;8), or t(8;22), and with a phenotype indicating mixed lymphoid-myeloid leukaemia (also called biphenotypic leukaemia). Poor prognosis tumour biology, particularly Ph+ ALL is more common among older adults, seen in up to 50% of older ALL patients.

The initial goal of therapy for adult ALL is to correct problems secondary to bone marrow failure; that is, to treat anaemia with blood transfusions, treat documented or suspected infection, and control bleeding. Specific anti-leukaemia treatment is then directed toward the achievement of a complete remission. Induction chemotherapy therapy for ALL, very different from that for AML, usually includes the use of prednisone, vincristine, daunorubicin, and asparaginase.[29] While these drugs are well tolerated in children, increasing age is associated with poorer drug tolerance. Mortality, usually from infection and/or bleeding during the induction process, may occur in 10–20% of elderly patients.

It is widely accepted that patients with ALL require therapy after complete remission (CR).These phases of treatment once the patient is in CR have been referred to as intensification (consolidation) therapy and maintenance therapy. The optimal therapy after remission and the duration of such therapy in older patients are not clearly defined. Most programmes use multiple drugs administered in a cyclic fashion over a two-year period; the more intensive therapy is given over about six months after CR is achieved (intensification or consolidation), followed by a less-intensive outpatient maintenance regimen for approximately 18 months.

Directed treatment to the craniospinal axis [central nervous system (CNS) prophylaxis] is standard practice in the treatment of childhood ALL. While the incidence of CNS leukaemia is lower in adults than in children, treatment to the CNS is also part of ALL therapy in adults. This usually consists of intrathecal methotrexate in conjunction with high-dose systemic therapy such as high-dose methotrexate and Ara-C, or cranial radiation.

With the above intensive treatment plan, the median duration of remission is approximately two years, with 35–45% of adult patients disease-free at five years. However, prognosis is poorer for older adults with long-term survival <20% with treatment.[30] One contributing feature to this poorer response duration in adults as opposed to children is the inability to deliver optimal chemotherapy at maximal doses due to comorbid diseases and increased

susceptibility to toxicity. This is evident both in the induction phase and during intensification post-remission with high treatment-associated mortality.[30]

Identification of targeted therapeutic approaches may improve outcomes for older adults with ALL. One example of this is the shifting treatment paradigm for the Ph+ ALL subtype. Outcomes for all patients with this poor prognosis variant have improved with the addition of imatinib mesylate to combination chemotherapy.[31] Imatinib mesylate inhibits the constitutively active abl tyrosine kinase which is seen in approximately half of older adults with ALL. Use of imatinib with steroids alone has demonstrated activity among older adults[32] and provides an option for patients who may not be candidates for aggressive chemotherapy due to comorbidity or poor functional status.

In summary, ALL is an uncommon disease that requires aggressive and prolonged chemotherapy for cure. Outcomes remain poor among older adults and treatment decision- making should be individualized based on tumour biology, estimated reserve capacity in response to treatment, and life expectancy. Standard multidrug chemotherapy (with imatinib for Ph+ ALL) should be considered for older adults with minimal comorbid disease and good functional status. The risks of treatment morbidity and mortality increase for older adults with poor functional status and/or limiting comorbid conditions. In this setting, palliative treatment with steroids, low-intensity chemotherapy, and imatinib for Ph+ ALL may be appropriate.

Conclusion

Myelodysplastic syndromes are common among older adults and the natural history varies greatly. Older adults with low-risk disease can be managed with supportive care alone for many years while those with higher risk disease, and good functional status should be considered for low-intensity therapy. The goal of therapy is to maximize quality of life, delay progression to AML and improve survival. AML is an aggressive disease requiring rapid initiation of multiagent chemotherapy for cure. While treatment outcomes remain suboptimal for older adults, selected older patients can benefit and be cured of disease. Older adults with good functional status and minimal comorbid conditions should be referred for treatment of AML. Similarly, selected older adults can benefit from treatment of ALL, although treatment courses are protracted. Curative and palliative treatment options have expanded for ALL with the use of targeted imatinib therapy for Ph+ ALL. Ongoing research aimed at identifying less toxic therapies targeted to tumour biology will likely expand treatment options for each of these disease entities for older adults.

Key points

- Myelodysplastic syndromes (MDS) are common and have a varied natural history.
- Older adults with low-risk MDS can be managed supportively.
- Treatment with low-intensity chemotherapy (i.e. 5-azacytidine or decitabine) should be considered for older adults with high-risk MDS and adequate functional status.
- Older adults with AML are more likely to present with aggressive tumour biology and treatment outcomes remain poor.
- Treatment for AML should be individualized. Older adults with favourable/intermediate tumour biology and good functional status can benefit from curative therapy.
- ALL is uncommon in older adults. Curative treatment is protracted but should be considered for those with good functional status. Imatinib should be part of curative or palliative therapy for Ph+ ALL.

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SECTION 4

Cardiovascular Diseases and Health

CHAPTER 34

Epidemiology of heart disease

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Introduction

Epidemiology is defined as the study of occurrence and distribution of disease in human populations. Epidemiological research can be used to study benefits of interventions to prevent and decrease the burden of disease or to predict requirements for trained healthcare professionals, caregivers for disabled or older people, and service planning. Coronary heart disease (CHD) is an important cause of morbidity and mortality. Incidence and prevalence of CHD both rise steeply with increasing age. The older population is growing and the world's population ≥60 years old is estimated to reach 2 billion by 2050 (three times that in 2000). The development and progression of atherosclerosis is not just a function of ageing but is determined by the distribution of cardiovascular (CV) risk factors related to specific lifestyles. Heart disease may affect quality or quantity of life or both. As the population suffering from heart disease becomes older, their functional ability becomes more important. Mortality cannot be the only outcome relevant to older people but quality of life, cognitive and functional capacities are equally important endpoints. While CHD is a major cause of mortality, other heart diseases may have a significant impact on quality of life due to limitation of exercise tolerance. This chapter discusses epidemiological features of the most common heart diseases affecting older people including CHD, heart failure, valvular heart disease and rhythm disorders (Box 34.1).

Box 34.1 Common heart diseases in older people

- Coronary heart disease
- Heart failure
- Valvular heart disease
  - *Degenerative valve disease*
  - *Infective valve disease*
- Rhythm disorders
  - *Atrial fibrillation*
  - *Sudden cardiac death*

Coronary heart disease

The CHD epidemic started in the 1950s affecting firstly western countries. Prior to the 1920s CHD was not common and caused only <10% of all deaths in the United States. However, by the 1950s this had escalated to >30% and it is now the leading cause of death. While its mortality has fallen by 50%, its incidence has decreased little or hardly at all. Mortality from CHD has also decreased among elderly persons, but information on changes in incidence in the elderly is limited. The main reasons for the decline in morbidity and mortality are due to changes in risk factors as well as improvement of treatment. Survival after myocardial infarction has improved and significant advances have also been made in the surgical and medical treatment of CHD.

Risk factors and prevention

Major risk factors for atherosclerosis have been well established. Epidemiological studies concluded that the causes for this epidemic are due to genetic factors in addition to other considerations such as age, smoking, hypertension, obesity, diabetes and cholesterol. Variations in disease occurrence in different nations still remain far from being fully explained. No single factor is responsible for CHD. It is a multifactorial disorder that is likely to be due to subclinical inflammation that many factors can contribute to, such as chronic infection, increased clotting tendencies and other irritants.

Genetics

It is believed that CVD results from many genes, each with a relatively small effect working alone or in combination with other modifier genes and/or environmental factors. Familial hypercholesterolaemia and hyperhomocystinuria are well-described examples. Insulin-like growth factor-1

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

(IGF-1) is believed to influence ageing and may be involved in the pathogenesis of CHD; however, a causative association is lacking. In the prospective (four-year) case-control study nested within the British Women's Heart and Health Study, IGF-1 was inversely correlated with waist:hip ratio, fasting insulin, C-reactive protein, triglycerides and systolic blood pressure, and was positively correlated with HDL cholesterol but there was no evidence of CHD risk reduction in older women (60–79 years old).[1] However, in another study high IGF-1 was independently associated with increased all-cause mortality and risk of development of heart failure in an elderly cohort of 642 individuals, aged 50–89 years, followed up for five years.[2] Telomere length is another genetic factor associated with CV health and ageing. Telomere attrition is associated with elevated blood homocysteine and increased endothelial cell inflammatory markers and may underlie early fetal origins of CVD. The identification and characterization of genes that enhance prediction of disease risk and improve prevention and treatment of atherosclerosis need further genetic epidemiological studies.

Age and sex

Prevalence of CHD increases with age from 2% for males and 0.5% for females at age 40–44 to peak at 18% and 12% respectively at age 85–89. Median age at onset is 67.5 years for males and 77.5 years for females. Lifetime risk is 35% for males and 28% for females. Prevalence of CHD decreased in individuals <65 and increased among those ≥75 years especially in women. CHD accounts for 22% of male deaths and 17% female deaths at all ages. Largely, epidemiology of CHD is changing from a fatal disease of middle-aged men to a more chronic condition of elderly women. CHD is intimately related to normal ageing in that its incidence continues to increase indefinitely with age. In a prospective study to investigate the influence of increasing age on incidence of CVD in 22 048 male physicians aged 40–84 who were free of major disease, incidence of CVD continued to increase to age 100 over 23 years of follow-up.[3] Beginning at age 80, CVD was more likely to be diagnosed at death. The remaining lifetime risk of CVD at age 40 was 34.8%, 95% confidence interval (CI), 33.1–36.5% and at age 90 was 16.7% (95% CI, 12.9–20.6%). These findings suggest that people aged ≥80 may be living with a substantial amount of undiagnosed CVD. Additional research is needed to determine if continued screening and detection of CVD up to and beyond age 80 might help improve health in later life.

Ethnicity and race

Prevalence of CHD and related risk factors vary among different ethnic groups. The pattern of this variation is complex, and could be related to genetic or socioeconomic differences. For example, populations of African descent living in Europe and the United States have a higher incidence of stroke and lower incidence of CHD than in their white counterparts. They have higher rates of hypertension, which may explain their high rate of stroke. Similarly, in China mortality from CHD is still lower than in western countries while mortality due to stroke is several times higher largely due to the high prevalence of hypertension. The lower rate of CHD may be explained by low rates of other risk factors including smoking.[4] In the Indian subcontinent CVD is expected to increase rapidly and it will be the host of >50% of cases of heart disease in the world within the next 15 years. Risk factors for this epidemic are similar to those elsewhere in the world; however, ~50% of CHD-related deaths occur in people <70 years compared with only 22% in the west. Also Asians living in western countries have a 50% greater premature mortality risk from CHD than the general population.

Diet

Dietary factors are related to the risk of CHD through several biological mechanisms. For example: (i) Fish consumption provides cardio-protective benefits through favourable effects on lipid profile, threshold for arrhythmias, platelet activity, inflammation, endothelial function, atherosclerosis and hypertension. Consumption of fish 1–2 times per week or at least 5–10% of energy from polyunsaturated fatty acids reduces the risk of CHD in older people relative to lower intakes.[5] (ii) Antioxidants present in fruit and vegetables improve endothelial function, inhibit platelet activation and lower blood pressure. (iii) High salt consumption is directly related to hypertension, myocardial infarctions and strokes. Modest reductions in salt lower systolic blood pressure by at least 2 mmHg reducing the prevalence of hypertension by 17%, cardiac events by 30% and overall mortality by 20%. Older people will gain the greatest advantage from lowering their salt intake, most likely because they are more salt sensitive. (iv) Alcohol intake has a U-shaped relationship with the risk of CHD. 'Moderate drinking' defined as one drink for women and two drinks for men per day reduces the risk of CHD by 25%. Data relating to multivitamin use and the risk of CVD are inconsistent. Broader adherence to recommendations for daily intake of fruit, vegetables, low salt, alcohol in moderation and fish may take away 20–30% of the burden of CVD and result in one extra life-year if started early by the age of 40 years.[6]

Cholesterol

Cholesterol is a risk factor for CVD in the middle aged but appears to be less potent at older ages. However, dietary cholesterol is more detrimental in people with diabetes, regardless of age, because of dyslipidaemia and increased insulin resistance. In the Health, Ageing and Body Composition Study of 1941 community-dwelling elderly people

aged 70–79, there were no significant associations between dietary fats and CVD risk, hazard ratio (HR) 1.47, 95% CI, 0.93–2.32 for the upper versus lower tertile, p for trend 0.10 after nine years of follow-up. However, dietary cholesterol was associated with increased CVD risk among older people with diabetes (3.66, 1.09–12.29).[7] Possible reasons for these results are attenuated association between lipids and CV risk among older people, differences in baseline CV risk between old and young, or selective survivorship of older people leading to a population sample less vulnerable to environmental factors such as dietary fat.

Exercise

Although few studies have been conducted in the elderly, most have reported physical activity to be beneficial in preventing premature mortality but with some concerns about adverse effects especially in frail elderly with comorbidities. Physical activity may trigger sudden death and may have a higher risk of injury. However, in a Japanese study of 10 385 elderly (aged 65–84), most of whom were under treatment for pre-existing disease, every physical activity was associated with a reduced risk of all causes and CVD mortality after seven years of follow-up. Hazard ratios (95% CI) for CVD mortality among participants with ≥5 days of physical activity per week for the total sample and those with pre-existing diseases were 0.38 (0.22–0.55) and 0.35 (0.24–0.52) respectively, compared with no physical activity. In spite of possible adverse effects, this study indicated that elderly people with a pre-existing disease benefit from any level of physical activity in a dose-response relationship to mortality.[8]

Obesity

Obesity is a risk factor for CHD, poor health and excess mortality. Thresholds for normal weight or obesity defined as body mass index (BMI) were primarily based on evidence from studies in younger adults. In older people the relationship between weight and CV risk is more complex. It remains unclear whether overweight and obese cut points are overly restrictive measures for predicting mortality in older people. In a study to examine all cause and cause-specific mortality associated with underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obesity (BMI > or = 30.0) in an elderly cohort of 4677 men and 4563 women aged 70–75, mortality risk was lowest for overweight participants after 10 years of follow-up. Risk of death for overweight participants was 13% less than for normal weight participants (HR 0.87, 95% CI, 0.78–0.94). Minimum mortality risk was found at a BMI of 26.6 (95% CI, 25.7–27.5) in men and 26.26 (95% CI, 25.5–26.9) in women. Risk of death was similar for obese and normal weight participants (HR 0.98, 95% CI, 0.85–1.11).[9] It appears that extreme obesity is harmful but overweight older people are not at greater mortality risk, and there is little evidence that dieting in this age group confers any benefit.

Smoking

Smoking is a major modifiable risk factor for CVD and causes 11% of all CVD-related mortality. Smoking contributes to the pathogenesis of CHD through promotion of atherosclerosis, triggering of coronary thrombosis, coronary artery spasm, cardiac arrhythmias and the reduced capacity of blood to deliver oxygen. The magnitude of the burden produced by smoking increases rather than decreases with ageing. While relative risk for smoking on CHD is similar in the elderly and middle aged, there is a twofold increase in excess absolute risk in the elderly. Benefits of cessation for older smokers are similar in magnitude to those of younger smokers who quit. The risk of CHD drops by 50% one year after smoking cessation and approaches that of a person who has never smoked within 3–4 years, even in individuals older than 60 years. Smoking cessation is highly cost-effective and should be viewed as a therapeutic rather than just a preventive intervention regardless of age.[10]

Socioeconomic factors

There is an inverse relationship between socioeconomic status (SES) and prevalence of CV risk factors. People with lower SES tend to adopt unhealthier behaviours, such as smoking and unhealthy dietary habits, and seem to have an increased prevalence of CV risk factors resulting in socioeconomic inequalities in CV health. Although there is a strong social class gradient in CHD risk in middle age, the evidence in old age is limited. In a population-based study of 3761 British men aged 60–79 years there was a graded relationship between social class and CHD incidence after 6.5 years of follow-up. The HR for CHD incidence comparing social class V (unskilled workers) with social class I (professionals) was 2.14 (95% CI, 1.06–4.33; p for trend = 0.11) after adjustment for behavioural factors. Absolute difference in CHD risk between highest and lowest social classes was 4%. Socioeconomic inequalities in CHD persist in the elderly and are at least partly explained by behavioural factors. Improving behavioural factors (especially smoking) could reduce these inequalities by one third.[11]

Hypertension

Hypertension is a major risk factor for CVD in elderly. It reduces life expectancy by seven years. Prevalence of hypertension is 20% in developed countries. However, prevalence is significantly higher in older people affecting 70% of those >80 years. Black Americans develop hypertension earlier in life and it tends to be more severe than in the white population. There is a strong but complex association between blood pressure (BP) and

age. Up to 50 years of age, systolic and diastolic BP rise in tandem. After age 50, systolic BP continues to rise, whereas diastolic BP tends to fall. Below age 50, diastolic BP is the major predictor of CHD risk, whereas above age 60, systolic BP is more important. There is also an enhanced risk for CHD associated with increased pulse pressure. The risk of a fatal CHD event doubles for every 20/10 mmHg increment above 115/75 mmHg. Absolute risk of adverse outcomes increases with age reaching 16-fold higher for persons 80–89 years than for those 40–49 years. A 10 mmHg reduction of systolic BP would predict a 50–60% lower risk of stroke death and a 40–50% lower risk of CHD death. In very old individuals (≥85 years old) the association between hypertension and mortality is weaker and treating hypertension reduces risk of death by 21%, risk of stroke by 30% and risk of cardiac failure by 64%. The target for BP is <140/90 mmHg in general and <130/80 mmHg in individuals with diabetes or chronic kidney disease. Evidence that excessive lowering of diastolic BP in older hypertensive individuals with wide pulse pressures may compromise cardiac outcomes (J curve) is inconsistent and no consensus exists regarding the minimum safe level of diastolic BP in these individuals.[12]

Diabetes mellitus

Diabetes has been recognized as an independent major CV risk factor. In spite of various known metabolic and microvascular complications of diabetes, cardiovascular disease remains the most common cause of death in diabetic persons of all age groups affecting around 65–80%. Diabetes itself, in the absence of associated CHD constitutes a risk similar to those of non-diabetic individuals with a previous history of myocardial infarction. Increased risk of CVD in diabetes is not fully explained by traditional risk factors and could be related to increased insulin resistance. Risk of CHD and myocardial infarction rises by 30% and 14% respectively for every 1% increase in HbA1c. Whether hyperglycaemia itself is a risk for CHD is not very clear. Hyperglycaemia leads to an increase in oxidative stress which, in combination with other risk factors, may cause an accelerated progression of atherosclerosis.

Metabolic syndrome

Metabolic syndrome is a constellation of central obesity, impaired fasting glucose, hypertension, high triglycerides and low HDL cholesterol. Pathophysiology of metabolic syndrome includes decreased physical activity and increased inflammation. In older people vitamin D deficiency,[13] leading to increased parathyroid hormone and insulin resistance, in combination with low testosterone, leading to increased waist:hip ratio, are other contributing factors. Metabolic syndrome affects >40% of persons >60 years old and is more common in men. Comparative utility of metabolic syndrome versus its individual components for predicting adverse outcomes in older populations is not well established. In an Italian study of 2910 subjects aged ≥65 years, metabolic syndrome was associated with increased all-cause mortality in all subjects (HR 1.41, 95% CI, 1.16–1.72, $p < 0.001$), in men (1.42, 1.06–1.89, $p < 0.017$), and in women (1.47, 1.13–1.91, $p < 0.004$). It was also associated with increased CV mortality in all subjects (1.60, 1.17–2.19, $p < 0.003$), in men (1.66, 1.00–2.76, $p < 0.051$), and in women (1.60, 1.06–2.33, $p < 0.025$). Among metabolic syndrome components, all-cause mortality is better predicted by high glucose in all subjects (1.27, 1.02–1.59, $p < 0.037$) and in women (1.61, 1.16–2.24, $p < 0.005$) and by low HDL cholesterol in women (1.48, 1.08–2.02, $p < 0.014$), whereas CV mortality is better predicted by high glucose (2.17, 1.28–3.68, $p < 0.004$) and low HDL cholesterol (1.78, 1.07–2.95, $p > 0.026$) in women.[14] In a similar US study of 4258 older people ≥65 years free of CVD, those with metabolic syndrome had a 22% higher mortality, relative risk (RR) 1.22, 95% CI, 1.11–1.34 compared with persons without metabolic syndrome after multivariable adjustment. Higher risk with metabolic syndrome was confined to persons having an elevated fasting glucose level >6.1 mmol l^{-1} (RR 1.41, 95% CI, 1.27–1.57) or hypertension (RR 1.26, 95% CI, 1.15–1.39) as one of the diagnostic criteria of metabolic syndrome. Persons having metabolic syndrome without high fasting glucose or metabolic syndrome without hypertension did not have higher risk (RR 0.97, 95% CI, 0.85–1.11 and 0.92, 0.71–1.19 respectively). Persons having both hypertension and high fasting glucose had 82% higher mortality (RR 1.82, 95% CI, 1.58–10.9).

In older people individual components of metabolic syndrome predict CVD mortality with equal or higher HR when compared with metabolic syndrome. Therefore, these findings suggest that the metabolic syndrome concept is a marker of CVD risk, but may not have any more advantage in predicting cardiac risk than its individual components.[15]

Frailty and disability

Frailty is a geriatric syndrome of increased vulnerability to stress factors due to decline in function in multiple interrelated systems. Frailty is distinct from related concepts of (i) comorbidity: the burden of coexisting medical illnesses, and (ii) disability: the limited ability for self-care (Figure 34.1). Frailty reflects biological rather than chronological age leading to substantial variability in the outcomes of older people. The relationship between frailty and CVD is mutual; frailty may lead to CVD just as CVD may lead to frailty. In other words frailty is associated with CVD as a risk factor and as an outcome. Around 7% of the US population >65 years and 30% of octogenarians are frail. Domains to define frailty include mobility, strength, balance, motor processing, cognition, nutrition, endurance

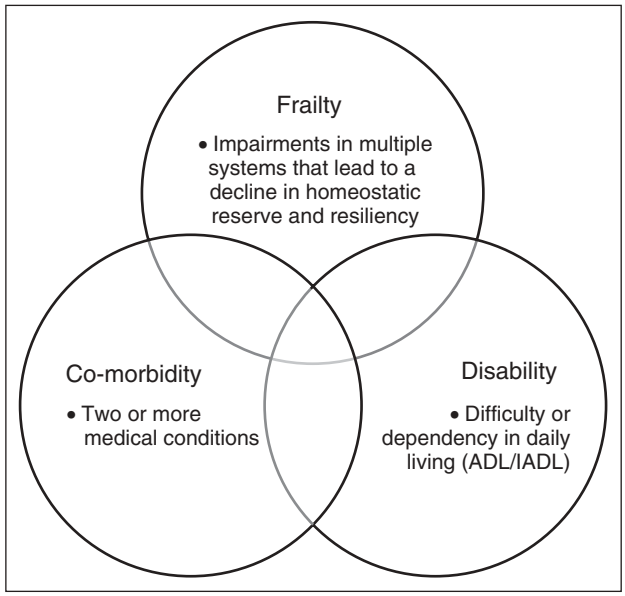

Figure 34.1 Overlap between frailty, comorbidity, and disability. ADL, activities of daily living (basic self-care tasks); IADL, instrumental ADL (household management tasks). Reprinted from Afilalo *et al.*[16] Copyright 2009, with permission from Elsevier.

Table 34.1 Association between cardiovascular disease and frailty.

Study	Variable
	Prevalent frailty in elders with CVD
Zutphen Elderly Men's Study	OR 4.1 (95% CI, 1.8–9.3)
CHS	OR 2.79 (95% CI, 2.12–3.67)
Beaver Dam Eye Study	OR 2.67 (95% CI, 1.33–5.41)
WHI-OS	OR 3.36 (95% CI, 3.09–3.66)
WHAS I and II	OR 2.72 (95% CI, 1.72–4.30)
	Incident frailty in elders with CVD
WHI-OS	OR 1.47 (95% CI, 1.25–1.73)
	Incident CVD in frail elders
HABC Study	HR 1.61 (95% CI, 1.05–2.45)
	Mortality in frail elders with severe CVD
Cacciatore *et al.*	HR 1.62 (95% CI, 1.08–2.45)
Purser *et al.*	OR 4.0 (95% CI, 1.1–13.8)

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and physical activity. Frailty reduces patients' ability to maintain homeostasis in the face of acute stress, predicts mortality and heralds transition to disability. In a systematic review of frailty in patients with CVD, nine studies were included encompassing 54 250 elderly patients with a mean follow-up of 6.2 years. In community-dwelling elders, CVD was associated with an odds ratio (OR) of 2.67 to 4.1 for prevalent frailty and an OR of 1.47 for incident frailty in those who were not frail at baseline. Gait velocity (a measure of frailty) was associated with an OR of 1.61 for incident CVD. In elderly patients with documented severe CHD or heart failure, the prevalence of frailty was 50–54%, and this was associated with an OR of 1.62 to 4.0 for all-cause mortality after adjusting for potential confounders (Table 34.1). It is likely that underlying abnormalities in haematological, inflammatory and metabolic systems in frail older patients are linked to increased CV risk. Compared with non-frail counterparts, frail patients had significantly higher levels of factor VIII, D-dimers, C-reactive protein, leukocytes, fibrinogen, glucose, low vitamin D and low haemoglobin. The close correlation between frailty and biomarkers of inflammation and thrombosis resembles the correlation between CVD and these same biomarkers. This common biological pathway may explain why frailty and CVD are interrelated at clinical level. Reasons to consider frailty in older people with CVD include its early identification and anticipation of care after major cardiac events. There is overlap of frailty with comorbidity and disability. Unintended weight loss, disability in activities of daily living and presence of multiple comorbid conditions in a complex cardiac patient should alert physicians to the possibility of associated frailty. Screening of frailty may include simple tests, such as grip strength, gait speed or quadriceps strength. Early recognition of frailty will need comprehensive geriatric assessment combined with multidisciplinary interventions to slow or reverse functional decline, improve physical performance and quality of life.[16] Disability, on the other hand, is a common condition in older people and has been associated with prevalent CHD and shorter longevity. It is less clear whether disability is a risk factor for atherosclerosis development or a prognostic factor for CHD outcome. In a French multicentre prospective population-based cohort of 9294 subjects free of CVD (aged $\geq$65 years), the mean level of CV risk factors increased gradually with severity of disability. After a median follow-up of 5.2 years, 264 first coronary events, including 55 fatal events, occurred. After adjustment for CV risk factors, participants with moderate or severe disability had a 1.7 times (95% CI, 1.0–2.7) greater risk of overall CHD than non-disabled subjects, whereas those with mild disability were not at greater CHD risk. An association was also found with fatal CHD, for which risk increased gradually with severity of disability (HR 1.7, 95% CI, 0.8–3.6 for mild disability, 3.5, 1.3–9.3 for moderate to severe disability, p for trend = 0.01). This result reflected a specific association between disability and fatal but not with non-fatal CHD. The lack of association between disability and non-fatal CHD suggests that disability has little impact on atherosclerosis development. In other words disability even of mild severity has more to do with prognosis rather than with occurrence of CHD (Figure 34.2). However, this prognostic function of disability could be related to the possibility that disabled subjects suffering from an acute

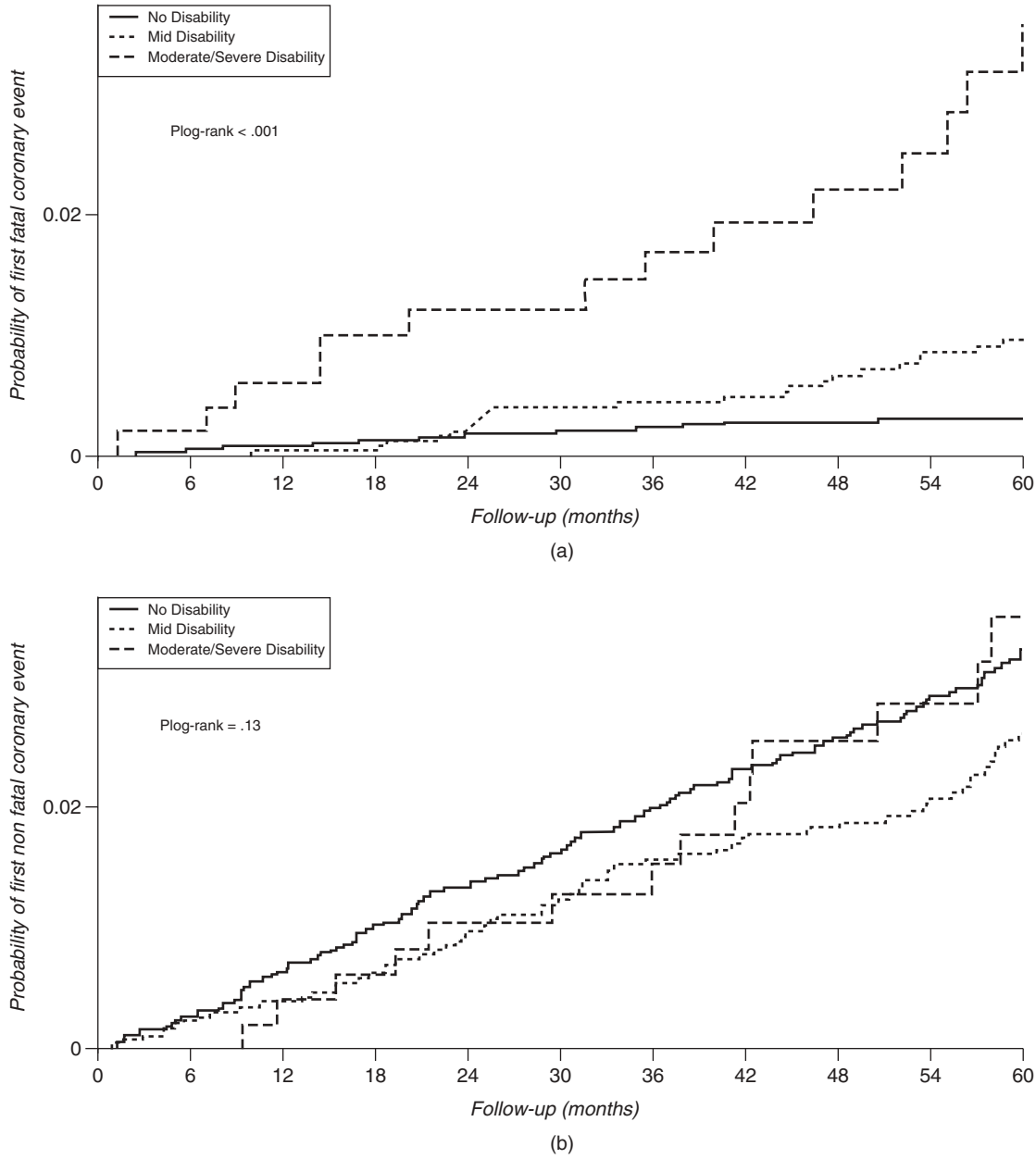

Figure 34.2 (a) Unadjusted Kaplan-Meier cumulative probability of incident fatal coronary heart disease over six years of follow-up according to baseline degree of disability. The Three-City Study. (b) Unadjusted Kaplan-Meier cumulative probability of incident non-fatal coronary heart disease over six years of follow-up according to baseline degree of disability. The Three-City Study. No disability (n = 54 080); mild disability: disability in mobility only (n = 52 712); moderate or severe disability: disability in mobility plus activities of daily living, instrumental activities of daily living, or both (n = 5562). Reproduced from Plichart *et al.*[17] with permission from Wiley-Blackwell.

event might be treated less aggressively, too frail to cope with a vascular event and likely to die, or simply disability is associated with severe CHD with a worse prognosis. Therefore, in this population, promotion of regular physical activity seems appropriate, because physical activity has been associated with less severe acute coronary syndrome, lower in hospital mortality, better short-term prognosis and less disability.[17]

Risk factors in the cognitively impaired

Little is known about CV risk factor profile for older people with dementia. As many CV risk factors are treatable by lifestyle changes, confirmation of the risk factor profile for older people with dementia could substantially impact upon preventive health practices for this group of patients. People with dementia often lack the ability to notice or address symptoms of disease and may not be

able to understand or be appropriately concerned about vascular risk factors and may need a more active approach than the general population does. In a cross-sectional study of 470 older people with dementia (age 50–90 years), healthy behaviour was low with 98.9% of participants having an unhealthy diet and 68.3% a lack of exercise. Smoking (13.6%) and alcohol abuse (0.3%) were relatively minor problems. Abdominal overweight (70.4%), hypertension (36.8%), hypercholesterolaemia (31.8%) and diabetes (8.7%), were highly prevalent.[18] In another study of 155 individuals attending a specialized ageing clinic, risk factor assessments found 18% with hypertension, 8% with elevated glucose, 27% with elevated total cholesterol, 70% overweight or obese, 11% current or ex-smokers and 96% with inadequate daily exercise. The prevalence of hypertension and smoking increased significantly with age.[19] These profiles have important implications in determining the risk of CVD in these patients. Campaigns to promote health should consider the introduction of preventive screening programmes in patients with dementia.

Reverse epidemiology

Reverse epidemiology refers to paradoxical epidemiological associations between survival outcomes and traditional CV risk factors such as obesity, hypertension and hypercholesterolaemia. It has been observed in chronic wasting disease states such as chronic heart failure, dialysis patients, advanced malignancies and in advanced age. The relation between these traditional risk factors and poor outcomes exists but in the opposite direction. For example, higher BMI, higher blood pressure, as well as high cholesterol are associated with improved heart failure outcomes. In patients with diabetes and heart failure tight diabetes control (HbA1c < 7%) is associated with higher mortality in comparison to HbA1c > 7% in accordance with reverse epidemiology phenomenon. Relative risk associated with higher BMI decreases substantially in older age groups. Reverse epidemiology with respect to cholesterol levels has been demonstrated in the elderly; however, hypertension and poor glycaemic control in older people with diabetes remain associated with increased morbidity and mortality. In a study of 400 hospitalized individuals >60 years old, obesity did not show independent survival value. Obesity, higher blood pressure and serum cholesterol, besides being related to lower mortality both in hospital and after discharge, were associated with better nutrition and functional capacity, less intense acute phase reaction and organ dysfunction, and lower incidence of high mortality diseases such as dementia, pneumonia, sepsis or cancer. These associations may explain why obesity and other reverse epidemiology data are inversely related to mortality. The increased mortality is related to under-nutrition and frailty manifested by low cholesterol and low BP. In hospitalized patients, weight loss and malnutrition are frequent and must be attributed to disease and to inflammatory response. Diseases such as cancer, dementia or heart failure cause malnutrition, a predisposing condition for sepsis which is often the final cause of death. Patients with BMI <30 who died in hospital showed more weight loss than those who survived; the lower the BMI, the greater the weight loss. In contrast, patients with BMI >30 who died in hospital gained more weight than those who survived; the higher the BMI, the greater the weight gain. When BMI was <30, patients who died had lost more weight than survivors. However, above 30 the situation was the opposite: patients who died in hospital had gained more weight than those who survived. This change at 30 of the prognostic meaning of weight variation indicates a limit on the obesity paradox or a U-shaped relation.[20] Weight gain in patients with a BMI higher than 30 is unhealthy (since it is related to mortality) as is weight loss in patients with lower BMI. The U-shaped relationship between obesity and survival was also observed in community-dwelling older patients with heart failure. In a study to determine all-cause mortality for 1236 patients, mean (SD) age 71 (12) years with a prior diagnosis of heart failure and a preserved ejection fraction (≥50%) survival was better for groups with higher BMI up to a BMI >45 where the mortality increased. After adjustment for patient age, history, medications, and laboratory and echocardiographic parameters, the HR for total mortality (relative to BMI 26–30) were 1.68 (95% CI, 1.04–2.69) for BMI <20, 1.25 (95% CI, 0.92–1.68) for BMI 20–25, 0.99 (95% CI, 0.71–1.36) for BMI 31–35, 0.58 (95% CI, 0.35–0.97) for BMI 36–40, 0.79 (95% CI, 0.44–1.4) for BMI 41–45, and 1.38 (95% CI, 0.74–2.6) for BMI >45 ($p < 0.0001$) (Figure 34.3). Thus, despite the benefit of weight loss in the prevention of CHD and heart failure, there is a lack of data to support a survival benefit from weight loss in patients with established heart failure.[21] The mechanism for reverse epidemiology is not clear. It appears that malnutrition and inflammation are characteristics shared by populations exhibiting reverse epidemiology. In heart failure weight loss associated with increased inflammation is termed cardiac cachexia. In that sense heart failure is a 'systemic inflammatory disease'. It is also likely that low BMI, low cholesterol and low blood pressure associated with other factors such as low serum albumin and low serum iron are simply markers of poor health and chronic comorbid conditions which lead to poor outcomes. Clinical implication of this is not yet clear but more attention should be focused on optimal management of under-nutrition and inflammation. It is early to conclude that withdrawal of proven medications with survival benefits such as angiotensin-converting enzyme inhibitors or beta-blockers is recommended. Statins may have an anti-inflammatory effect that can be beneficial in management of inflammation irrespective of cholesterol-lowering effects. Reverse epidemiology questions the limits of normal

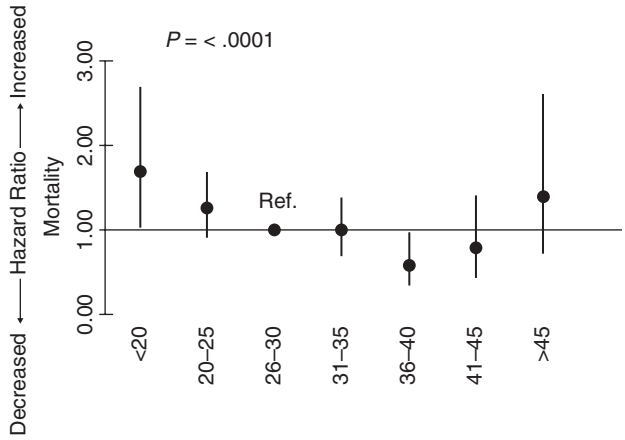

Figure 34.3 Hazard ratios for mortality by BMI after adjustment for age, history, medications, laboratory and echocardiographic findings (all $p < 0.0001$). A U-shape relationship persists between BMI and mortality. Reprinted from Kapoor *et al.*[21] Copyright 2010, with permission from Elsevier.

BMI (20–25) for ageing and chronic diseases. It seems appropriate, in diseased individuals, to restrain weight loss by improving feeding and maintaining physical activity to preserve muscle mass. Further research is still needed to clearly understand the mechanisms of reverse epidemiology to better care for these frail patients (Box 34.2).

Box 34.2 Summary – CHD

Epidemiologic features

- Incidence increases indefinitely with age.
- Relationship with obesity is U-shaped and inverse with socioeconomic status.
- Hypertension-related risk is 16-fold in persons 80–89 compared to 40–49 years.
- Metabolic syndrome does not add advantage in predicting CV risk above its individual components.
- Frailty is a non-conventional risk factor with a mutual relationship to CVD.
- Disability is a poor outcome indicator for CHD.
- In frail older people a paradoxical relation exists between traditional risk factors and outcome. The mechanism of this reverse epidemiology is related to malnutrition and inflammation.
- Reverse epidemiology questions the limits of normal BMI (20–25 kg m^{-2}) for ageing and chronic diseases.

Clinical implications

- Benefits of quitting smoking persist in older people.
- A 10 mmHg reduction in systolic BP would reduce CHD mortality by 50%.
- Early recognition of frailty is important to slow or reverse functional decline, improve physical performance and quality of life through multidisciplinary interventions.
- Attention should be focused on optimal management of under-nutrition and inflammation. It seems appropriate, in diseased individuals, to restrain weight loss by improving feeding and maintaining physical activity to preserve muscle mass.
- Physical activity has a positive impact on mortality in a dose-response relationship.

Heart failure

Heart failure is characterized by systolic or diastolic ventricular dysfunction associated with evidence of circulatory failure manifested by fatigue and fluid retention. It is becoming increasingly common and is the end product of CHD, hypertension and valvular heart disease. Therefore heart failure epidemiology is related to prevalence, incidence and outcomes of these CV diseases (Figure 34.4). It mostly affects elderly people as >75% of patients are >65 years old and mean age is 75 years. In developed countries the biggest factor boosting heart failure prevalence is increasing growth of an elderly population. In the United States, the number of elderly (>65 years) is expected to grow from 35 million in the year 2000 to 70.3 million in 2030. In the United Kingdom the number of people aged >65 years has increased by 50% and those >85 has increased threefold in the last 40 years. Even if incidence remains constant, the total number of people with heart failure is expected to double increasing its prevalence. Prevalence and incidence of heart failure in those aged 80–89 years is 10 times prevalence and incidence in those aged 50–59 years. In the United States 550 000 new cases of heart failure occur each year. More than 20 million people have heart failure worldwide of whom 5 million are in America and 6.5 million in Europe. Heart failure is the leading cause of hospitalization affecting >20% of acute hospital admissions of individuals >65 years. Age-adjusted annual incidence of heart failure is 0.14% in women and 0.23% in men, with better survival among women. Lifetime risk for developing heart failure at age 40 years is 21% for men and 20% for women. Several factors contribute to the increased burden of heart failure. Improved care of acute myocardial infarctions and of those patients already diagnosed with heart failure have combined to foster a growing epidemic. Age-adjusted survival rates have improved and risk of death has declined 12% per decade. However, heart failure still carries a grave prognosis. The two- and five-year mortality rates are 60% and 75% respectively. Mortality in heart failure is as high as in many common types of cancer such as bowel cancer in men and breast cancer in women. It is associated with a comparable number of expected life-years lost (6.7 years per 1000 in men and 5.1 years per 1000 in women).[22]

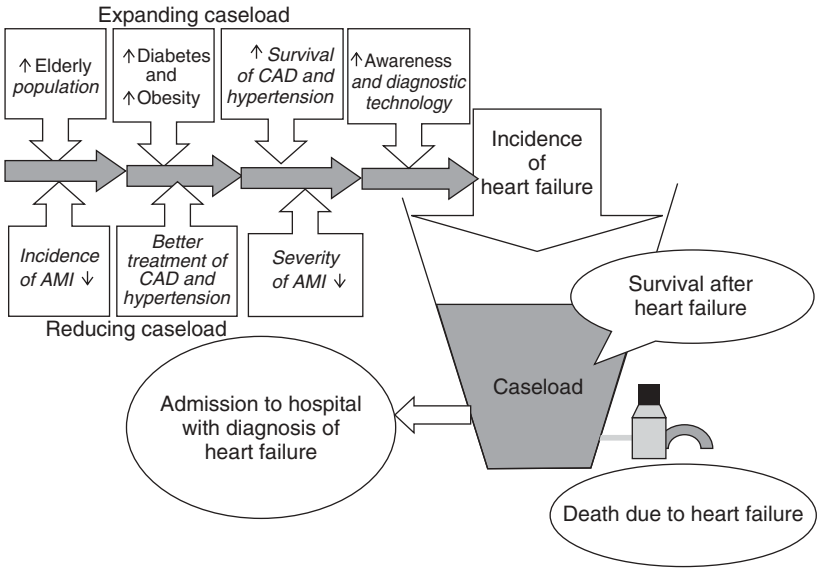

Figure 34.4 Epidemiology of heart failure. AMI, acute myocardial infarction; CAD, coronary artery disease. Reprinted from Najafi *et al*.[22] by permission of Oxford University Press.

Ethnic variations

In developing countries ischaemic aetiology for heart failure is less common. Other causes such as rheumatic (Africa, Asia, Latin America), Chagas disease (Latin America) and hypertension (African) are more prominent. Hypertension, rheumatic heart disease, cardiomyopathy, chronic lung disease and pericardial disease are the main contributors to the aetiology of heart failure in Africa, accounting for >90% of cases. In Arabic populations prevalence of heart failure is common and increases with age from 1 per 1000 in individuals <45 years to 25 per 1000 in those ≥65 years. Common causes are similar to those in western countries such as CHD and hypertension. However, idiopathic dilated cardiomyopathy is relatively more prevalent than reported in the West. Valvular heart disease and lung diseases causing heart failure are less common. Incident heart failure before 50 years of age is more common among blacks than among whites. Diastolic hypertension, obesity, lower HDL cholesterol and kidney disease are independent predictors. Although CHD and its complications remain uncommon in developing countries, the situation is changing due to modifications in lifestyle, diet, cultural attitudes and other consequences of rapid urbanization which will lead to a global rise in incidence and prevalence of heart failure.[23]

Risk factors and prevention

A large proportion of heart failure risk is attributed to modifiable risk factors. In the Health, Aging and Body Composition Study, 2934 participants were enrolled, mean (SD) age 73.6 (2.9) years, 47.9% men, 58.6% white, and 41.4% black and assessed for incidence of heart failure, population attributable risk (PAR) of independent risk factors for heart failure, and outcomes. During a median follow-up of 7.1 years, 258 participants (8.8%) developed heart failure (13.6 cases per 1000 person-years, 95% CI, 12.1–15.4). Men and black people were more likely to develop heart failure. No significant sex-based differences were observed in risk factors. CHD (PAR 23.9% for white and 29.5% for black) and uncontrolled hypertension (PAR 21.3% for white and 30.1% for black) carried the highest PAR in both races. Among black participants, six risk factors (smoking, increased heart rate, CHD, left ventricular hypertrophy, uncontrolled hypertension, and reduced glomerular filtration rate) had >5% higher PAR compared with that among white participants, leading to a higher overall proportion of heart failure attributable to modifiable risk factors in black compared to white participants (67.8% vs. 48.9%). Participants who developed heart failure had higher annual mortality (18.0% vs. 2.7%). No racial difference in survival after heart failure was noted; however, rehospitalization rates were higher among black participants (62.1 vs. 30.3 hospitalizations per 100 person-years, $p < 0.001$).[24] In another population-based case-control study of 962 Olmsted County residents with heart failure (mean age 75.4 years; 53.7% women who were older than men 78.3 vs. 72.1 years respectively, $p < 0.001$) mean (SD) number of risk factors for heart failure per case was 1.9 (1.1) and increased over time ($p < 0.001$). Hypertension was most common (66%), followed by smoking (51%). Risk of heart failure was particularly high for CHD and diabetes (OR 3.05, 95% CI, 2.36–3.95 and 2.65, 1.98–3.54) respectively (Table 34.2). However, PAR was highest for CHD and hypertension, each accounted for 20% of heart failure cases in the population, although CHD accounted for the greatest proportion of cases in men (PAR 23%) and hypertension was of greatest importance in women (PAR 28%). Preventing CHD and hypertension will have

Table 34.2 Association between heart failure and risk factors from case/control analysis.

			Population Attributable Risk (95% CI)		
Risk Factor	**OR (95% CI)**	***p* Value**	**Overall**	**Women**	**Men**
CHD	3.05 (2.36–3.95)	<0.001	0.20 (0.16–0.24)	0.16 (0.12–0.20)	0.23 (0.16–0.30)
Hypertension	1.44 (1.18–1.76)	<0.001	0.20 (0.10–0.30)	0.28 (0.14–0.42)	0.13 (0.00–0.26)
Diabetes	2.65 (1.98–3.54)	<0.001	0.12 (0.09–0.15)	0.10 (0.06–0.14)	0.13 (0.08–0.18)
Obesity	2.00 (1.57–2.55)	<0.001	0.12 (0.08–0.16)	0.12 (0.07–0.17)	0.13 (0.07–0.19)
Ever smoker	1.37 (1.13–1.68)	0.002	0.14 (0.06–0.22)	0.08 (0.00–0.15)	0.22 (0.07–0.37)

the greatest population impact in preventing heart failure. Sex-targeted prevention strategies might confer additional benefit.[25]

Diastolic heart failure

Diastolic heart failure is defined by the presence of signs and symptoms of heart failure, normal ejection fraction and evidence of abnormal left ventricular diastolic function. Echocardiographic studies in the community show that 50% of all patients with heart failure have preserved left ventricular systolic function. Prevalence of diastolic heart failure increases more sharply with age more than systolic heart failure. It is likely that age-related changes in diastolic function lower the threshold for expression of diastolic heart failure in elderly. Ageing is associated with a stiffening of large vessels and concentric hypertrophy of left ventricular myocardium with reduced early diastolic relaxation and filling rates. This combined ventricular-vascular stiffening may contribute to increased prevalence of diastolic heart failure in elderly persons. This ventricular-vascular stiffening occurs more steeply in women. It is very likely that systolic hypertension plays an important role in the genesis of diastolic heart failure by increasing both vascular and ventricular stiffness. Compared to those with reduced systolic function, patients with preserved systolic function are older, more often female, more likely to have hypertension associated with left ventricular hypertrophy and less likely to have CHD. Mortality rates are higher in these patients compared to age-matched controls without heart failure, but not as high as those in patients with reduced systolic function. In contrast, morbidity, as measured by hospitalization and re-admission, is substantial and comparable to that of patients with systolic heart failure.

Complexity and care for heart failure

Heart failure and cognition

Heart failure results in losses in memory, psychomotor speed, and executive function in 25% of patients. In a study to determine types, frequency and severity of cognitive deficits among patients with heart failure compared with age and education matched healthy participants and participants with major medical conditions other than heart failure in a sample of 414 participants (249 heart failure, 63 healthy and 102 medical participants), heart-failure patients had poorer memory, psychomotor speed, and executive function compared with healthy and medical participants. Significantly more heart-failure patients (24%) had deficits in three or more domains and heart failure severity was associated with more cognitive deficits. Multiple comorbidity, hypertension, depressive symptoms and medications were not associated with cognitive deficits. Older patients with more severe heart failure have more problems in executive function.[26] Future studies are needed to identify mechanisms for cognitive deficits in heart failure and to test interventions to prevent cognitive loss and decline. On the other hand, the presence of heart failure in a cognitively impaired individual further increases heart failure-related morbidity and affects functional outcomes and need for institutional care.

Heart failure and geriatric conditions

There is a high prevalence of geriatric conditions among older people with heart failure including urinary incontinence, falls and dementia. Each of these conditions suggests the presence of a high degree of disability. Geriatric conditions are strongly and independently associated with short- (30 days) and long-term (5 years) mortality among older patients hospitalized for heart failure. In a study of 62 330 hospitalized heart-failure patients, mean (SD) age 79.6 (7.8), mortality rates were 9.8% at 30 days and 74.7% at 5 years. Dementia and mobility disability, were among top predictors of short (OR 1.86, 95% C I, 1.73–2.01 and 1.96, 1.81–2.12, respectively) and long-term mortality (2.01, 1.84–2.19 and 1.78, 1.70–1.87, respectively). These results enhance the relevance of cognitive and physical disabilities in heart-failure patients.[27] Despite the ageing population and the fact that heart failure primarily affects older persons in whom many complex conditions coexist, current studies and guidelines have not incorporated routine assessment or management of geriatric conditions.

Heart failure in care homes

Prevalence of heart disease in care homes is expected to be higher than in the general population due to older and frailer populations living in these settings. Little data is available because care home residents are often excluded from epidemiological studies. In a systematic review of 10 studies, prevalence of heart failure was 20% (range 15–45%). This figure is higher than in the general population (3–13%); however it could be underestimated as both undetected and incorrect diagnosis of heart failure was common. The mean age of study populations ranged between 79–89 years. CHD and atrial fibrillation were the most common causes of heart failure. The level of associated comorbidities (dementia 9–73%, diabetes mellitus 11–38%, chronic obstructive pulmonary disease 12–36%, and hypertension 8–55%) among these patients was also high.[28] Accurate diagnosis of heart failure in these settings is difficult and hampered by concomitant comorbidity which often shows characteristic signs and symptoms similar to those of heart failure (e.g. breathlessness, ankle swelling and fatigue) making interpretation difficult. Early diagnosis and treatment may prevent progression of the disease and lead to improvement of disabling symptoms, ultimately resulting in an overall improvement in quality of life.

Care needs for heart failure

Older people with heart failure have higher rates of disability, geriatric conditions, nursing home admission, and often require a multifaceted approach of care. Promoting care delivery systems that provide a coordinated, multidisciplinary approach to older people with heart failure will be necessary to optimize care. It is important to recognize associated physical and cognitive dysfunction in heart failure patients in order to optimize care and outcome. Although geriatric conditions are chronic and incurable, physical therapy and exercise may improve mobility, and increased caregiver and nursing support can be implemented to help patients with dementia adhere to medications. Benefits of interventions to address mobility and dementia may also enhance patients' abilities to avoid or cope with other medical conditions such as falls. Older patients with severe heart failure may be severely distressed with poorly controlled symptoms. There is a growing realization that palliative and supportive care may play an important role in treatment and underpin services to improve quality of life.

Caregiver burden

Heart failure imposes a significant burden on patients, families, and the long-term care system. However, social support is associated with better outcomes of heart failure. Mechanism for such better outcomes could be due to social support for enhanced self-care such as adherence to medication and healthy behaviour. Social isolation and living alone on the other hand are associated with increased heart-failure mortality, morbidity and psychosocial distress independent of possible contributing factors such as depression and severity of heart failure. The responsibilities of providing care for heart failure patients can be overwhelming, and may lead to exhaustion and depression in caregivers who may have multiple health problems of their own. Caregivers may also experience distressing symptoms such as sleep difficulties related to patient's sleep problems. Caregiver outcomes are also important, which should include both their physical and emotional health (Box 34.3).

Box 34.3 Summary – Heart failure

Epidemiologic features

- Heart failure is the end product of CHD, hypertension, and valvular heart disease.
- Older people are main sufferers (mean age 75 years).
- Prevalence and incidence in people 80–89 is 10 times those 50–59 years.
- Increasing growth of older population and improved care for CHD is leading to a growing epidemic of heart failure.
- In spite of improved survival, heart failure still carries a grave prognosis.
- Ischaemic aetiology is less common in developing countries.
- Heart failure risk is attributed to modifiable risk factors particularly CHD in men and hypertension in women.
- Diastolic heart failure is more common in older women who are likely to have hypertension, left ventricular hypertrophy and less likely to have CHD. It carries similar morbidity but less mortality than systolic heart failure.

Clinical implications

- Preventing CHD and hypertension will have an impact on reducing heart failure.
- Complex conditions tend to coexist with heart failure and are independently associated with mortality. Guidelines should incorporate routine assessment and management of these geriatric conditions.
- Prevalence in care homes is high and associated with a high level of disability. Early diagnosis and treatment in these settings may prevent progression and improve quality of life.
- Heart failure imposes a significant burden on families. It will need a multifaceted care. Caregiver outcomes are also important, and should include both their physical and emotional health.

Valvular heart disease

Prevalence and incidence of rheumatic heart disease have declined in the developed world but are still common in developing countries mainly affecting younger populations. The most common valve diseases in the elderly are either degenerative or infective.

Degenerative valve disease

The aortic valve is most commonly affected and prevalence of degenerative aortic valve disease (DAVD) rises as life expectancy increases. About 95 000 valve procedures are performed each year in the United States, and DAVD is responsible for >25 000 annual deaths. Traditional risk factors associated with atherosclerosis such as age, diabetes and cholesterol have been implicated in the development of DAVD. Early stages of DAVD are similar to the active inflammatory process of atherosclerosis including basement membrane disruption, inflammatory cell infiltration, lipid deposition and calcification. Visceral obesity also has a role in the development and progression of DAVD. In addition, visceral obesity in combination with other metabolic risk factors has been associated with degenerative changes in bioprosthetic heart valves. It seems that DAVD is related to an atherosclerotic process where interactions between lipids, inflammation and valvular tissue play an important role in the development of valvular calcification. This concept is referred to as 'valvulo-metabolic risk'. Despite these common risk factors only 50% of patients with DAVD have significant CHD, and most patients with CHD do not have DAVD suggesting that some other factors are contributing to the development of DAVD. Association of these risk factors may have implications for therapeutic interventions such as statins or angiotensin-converting enzyme inhibitors that may delay or prevent progression of DAVD. However, although 60–70% of patients with DAVD have dyslipidaemia and are already receiving statins, a substantial percentage of these patients show rapid progression. This suggests that, targeting dyslipidaemia alone may not be sufficient but targeting whole metabolic risk could be more effective in slowing valve degeneration progression.

Infective valve disease

Valve infection or infective endocarditis affects patients with predisposing valvular abnormalities traditionally caused by rheumatic carditis, and streptococcus viridans is the most common pathogen. This presentation is still seen in developing countries where rheumatic heart disease is prevalent. In the western world the incidence of infective endocarditis is rising in the elderly population >65 years reaching around four times that of the general population. Factors accounting for this increase include the high prevalence of undiagnosed degenerative valve disease and increased use of invasive procedures and implanted medical devices. Infective endocarditis has a predilection for males, but the proportion of females affected progressively increases with age. Despite progress in diagnosis and treatment, mortality rates remain high reaching twice that of younger patients. Diabetes, gastrointestinal and genitourinary tract cancers are predisposing risk factors. Although the prevalence of *S. aureus* decreases with age, enterococci and *S. bovis* are emerging as major players of infective endocarditis in elderly patients.[29] The evaluation of gastrointestinal and genitourinary tract lesions frequently requires invasive procedures, which remain an important risk. These findings might affect antibiotic prophylaxis strategy by taking into account patient age in global risk assessment (Box 34.4).

Box 34.4 Summary – Valvular heart disease

Epidemiologic features

- Prevalence of DAVD increases with age.
- Traditional risk factors are associated with DAVD and referred to as 'valvulo-metabolic risk'.
- Incidence of infective endocarditis in elderly population is four times and mortality is twice that of younger patients. The high prevalence of DAVD and increased use of invasive procedures and implanted medical devices are the main risks.
- Gastrointestinal and genitourinary tract cancers are predisposing factors for bacteraemia (enterococci and *S. bovis*) causing endocarditis.

Clinical implications

- Targeting metabolic risk factors may have an effect on slowing valve degeneration progression.
- Antibiotic prophylaxis strategy should take into account patient age in patients undergoing invasive gastrointestinal or genitourinary procedures.

Rhythm disorders

Abnormal heart rhythm increases with age even in those with normal hearts. Prevalence rates of atrial and ventricular ectopy reach up to 100% in older people. Left ventricular dysfunction is associated with increased prevalence of ventricular ectopy. However, there is no association between the extent or complexity of ventricular ectopy and the presence or absence of significant CHD in the absence of left ventricular dysfunction, and prognosis is good. Epidemiological features of two important rhythm disorders are discussed in this section: atrial fibrillation and sudden cardiac death believed to be due to ventricular tachycardia.

Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is characterized by uncoordinated atrial activation with consequent loss of atrial mechanical function. Hypertension is the most important single risk factor for AF, conferring a 1.5-fold increased risk in men and a 1.4-fold increased risk in women. AF affects 10% of

people >80 and 20% of people ≥90 years. In developed nations, overall prevalence is 0.9% and number of people affected is projected to more than double over the next two decades. Incidence is 3 per 1000 person-years in men and 2 per 1000 person-years in women aged 55–64 years but increases exponentially with advancing age to 20–30 per 1000 patient-years in individuals ≥85 years. AF is 1.5 times more common in men than in women. However, onset of AF in women occurs at a later age than in men (65 vs. 60 years respectively). Life-time risk of AF is 1 in 4 for both sexes from age 40 years onwards. The incidence pattern of AF may show racial and geographical variations with white subjects having twice the incidence rate of African Americans. Also incidence and prevalence appear to be lower in Asia than in the United States or Europe. The number of people with AF may reach 12.1 million by 2050 assuming no further increase in incidence, and 15.9 million assuming the continued increase in incidence rate is present. This may still be an under-estimation as prevalence of sustained silent AF in people >65 years is believed to reach up to 60%. AF is associated with a doubling of mortality ranging from 1.3–1.8-fold for men and 1.9–2.8-fold for women. Thromboembolic stroke is the most serious complication, risk of which is increased five times in patients with AF. AF is responsible for 15% of cases of strokes. Annual risk of stroke due to AF is 1.5% among patients aged 50–59 years and increases to 23.5% in those >80 years with a similar AF-related stroke mortality rates. AF also increases risk of heart failure by 2–7-fold. As a result of increasing age and improved survival rates in patients with CHD, heart failure and hypertension, an increase in prevalence of AF is likely to be exponential and sustained in the foreseeable future. Prognosis of AF is likely to be influenced by appropriate treatment strategies such as the use of anticoagulation to reduce stroke risk as well as rate or rhythm control to prevent tachycardia-induced cardiomyopathy and heart failure.

Sudden cardiac death

Sudden cardiac death (SCD) refers to death from abrupt cessation of cardiac function due to cardiac arrest. It results from a lethal arrhythmia and usually occurs in a background of structural abnormality or CHD. The most accepted definition is sudden and unexpected death within an hour of symptom onset. Incidence of SCD is 4–5 million cases per year worldwide and 60% of cases are males. There are two well-established peaks in age-related prevalence of SCD, one during infancy representing sudden infant death syndrome and the second in the geriatric age group, between ages 75–85 years. Approximately 80% of SCD are attributed to CHD. Two major mechanisms of fatal ventricular arrhythmias could result in SCD: (i) Polymorphic ventricular tachycardia resulting from acute coronary ischaemia associated with plaque rupture and occlusion of one or more main coronary arteries in patients with relatively normal left ventricular function. (ii) Monomorphic ventricular tachycardia resulting from re-entrant loops around areas of scarred myocardium in patients with established ischaemic cardiomyopathy. Either arrhythmia, if untreated, will eventually degenerate into ventricular fibrillation and SCD. A diagnosis of severe left ventricular dysfunction is the best available predictor of SCD risk and ejection fraction remains the major criterion to stratify patients for defibrillator implantation. An implantable cardiovertor defibrillator is effective therapy in the prevention of SCD. However, severe left ventricular dysfunction affects <30% of all SCD cases in the community. Almost 50% of SCD cases has normal left ventricular function and the remaining 20% have either mildly or moderately decreased left ventricular systolic function (ejection fraction >0.35 and <0.50). Impaired kidney function, as measured by cystatin C, has an independent association with SCD risk among elderly persons without clinical CVD.[30] Risk of SCD in patients with CHD is multifactorial and one major factor is rupture of atherosclerotic plaque. By stabilization of vulnerable plaque with cholesterol lowering and anti-platelets medications or by coronary artery bypass surgery and percutaneous angioplasty significant decline in ejection fraction may be less common in the future. However, specific clinical risk predictors for patients with vulnerable plaque that is prone to rupture still need further studies (Box 34.5).

Box 34.5 Summary – Rhythm disorders

Epidemiologic features

- AF is the most common sustained cardiac arrhythmia.
- Hypertension is the most important risk factor for AF.
- AF affects 10% of people >80 and 20% of people ≥90 years.
- AF is 1.5 times more common in men than in women.
- It increases risk of thromboembolic stroke by 5 times, heart failure by 2–7 times, and mortality by 2 times.
- As a result of increasing age and improved survival in patients with hypertension, an increase in prevalence of AF is expected.
- Incidence of SCD is 4–5 million per year and 60% of cases are males.
- Approximately 80% of SCD are attributed to CHD.
- Ventricular tachycardia degenerating into ventricular fibrillation is the most likely cause of SCD precipitated by rupture of atherosclerotic plaque.

Clinical implications

- Prognosis of AF is likely to be improved by appropriate treatment strategies such as use of anticoagulation to reduce stroke risk as well as rate or rhythm control to prevent tachycardia-induced cardiomyopathy and heart failure.
- Stabilization of vulnerable plaques by treatment of risk factors, or by coronary interventions may reduce incidence of SCD.

Conclusion

The incidence and prevalence of heart disease are increasing. As a result of the growth in an older population, combined with improvement in treatment, an increase in the number of older people living with cardiac conditions is expected. With increasing urbanization and modification of lifestyle in developing countries, the increase in heart disease is global. Unconventional risk factors are emerging in older people such as frailty and disability, which have both a predictive and prognostic effect. In the very old and frail individuals there is reversal of the effect of traditional risk factors such as obesity, hypercholesterolaemia and hypertension. The mechanism of this reverse epidemiology is likely to be due to inflammation and malnutrition. This will have clinical implications in treating malnutrition and avoiding weight loss in this group of patients with promotion of physical activity. Once heart disease is established it is likely to be associated with both physical and cognitive dysfunction and a high risk of institutionalization. Targeted care for older patients with heart disease that is multidisciplinary in nature with a focus on the whole person and outcomes relevant to them such as quality of life is needed.

Key points

- Epidemiology of heart disease is shifting from middle-aged men to elderly women.
- As the older population is growing combined with improvements in treatment, as well as increasing urbanization in developing countries, a global rise in prevalence of heart disease is expected.
- Once heart disease is established it is likely to be associated with physical and cognitive disability and increased risk of institutionalization.
- Care needs for older people with heart disease should take into account their complex needs and outcomes relevant to them considering illness in the context of the whole patient rather than as a solitary entity.

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CHAPTER 35

Cardiac ageing and systemic disorders

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Introduction

Ageing is a highly heterogeneous process and deterioration in organ function, including the heart, often does not correlate well with chronological age. A complex mix of influences combine to influence cardiovascular function in older people, including intrinsic ageing, the cumulative effect of multiple underlying diseases, and many environmental or external influences (such as frequency and intensity of exercise, cigarette smoking and diet). Separating the effects of intrinsic ageing from subclinical disease is challenging, and teasing out the additional contributions of environmental and lifestyle exposures even more problematic. Accepting these difficulties, it is still important to have a basic knowledge and understanding of the effects of intrinsic ageing on the heart to enable accurate interpretation of the effect of systemic disease on cardiovascular function in older people (see Figure 35.1). 'Healthy' or intrinsic cardiac ageing is associated with gradual decline in organ function and homeostatic reserve. The effects include reduced maximal aerobic exercise capacity and a decreased threshold for clinical expression of many age-related cardiac and non-cardiac diseases. However, healthy cardiac ageing by itself should not cause symptoms or limit usual activities of daily living.

Although there is no uniform ageing heart phenotype, some general principles are apparent, and we have attempted to summarize these. In this regard there are established and emergent data from multiple sources including *in vitro* work, animal models and clinical studies. This chapter aims firstly to summarize effects of ageing on cardiac structure, function and homeostatic reserve. The potential impact of these changes on the manifestation of various systemic (non-cardiac) diseases is then considered.

Changes in cardiac structure with ageing

For most solid organs age-related atrophy is the norm; however, magnetic resonance imaging (MRI) studies of the ageing heart show approximately 10% increase in cardiac mass from the age of 20 to 80 years in both men and women;[1] the 'healthy' older left ventricle is characterized by an increased mass-to-volume ratio.[2] Autopsy series confirm a high prevalence of left ventricular hypertrophy (LVH) in elderly subjects.[3–5] This hypertrophy is caused mainly by increased impedance to left ventricular ejection due to reduction in elasticity and compliance of the aorta and large arteries with resultant higher systolic arterial pressures; age-related degenerative aortic valve disease with sclerosis and thickening of valve leaflets and proximal bulging of the interventricular septum may also contribute; however, the contribution of these changes to LVH has not been definitively proven.

Data on cardiac changes in very elderly subjects are limited, with small numbers studied and often apparently contradictory results. Varying results are at least in part explained by differing rates of underlying disease, with coronary artery disease particularly common in males and hypertension in females.[6] As a result, in unselected very elderly subjects, reduced left ventricular systolic function and wall motion abnormalities are over-represented in males while females are particularly likely to have ventricular hypertrophy, atrial dilatation and moderate-to-severe mitral and tricuspid valve dysfunction.

Studies in older populations comprehensively screened for cardiovascular disease, particularly hypertension and coronary artery disease, have generally shown that the morphological cardiac changes described above are less marked in disease-free older hearts.[6] For example in the longitudinal Framingham cohort study, the association of LVH with increasing age was explained mainly by higher blood pressure, overweight, smoking and diabetes mellitus.[7] These findings reinforce how difficult it is to distinguish between cardiac changes secondary to intrinsic ageing and changes as a result of disease or environmental exposures. It is likely that certain structural changes classically thought to be primarily manifestations of intrinsic ageing are in fact also influenced by lifestyle or environmental factors;

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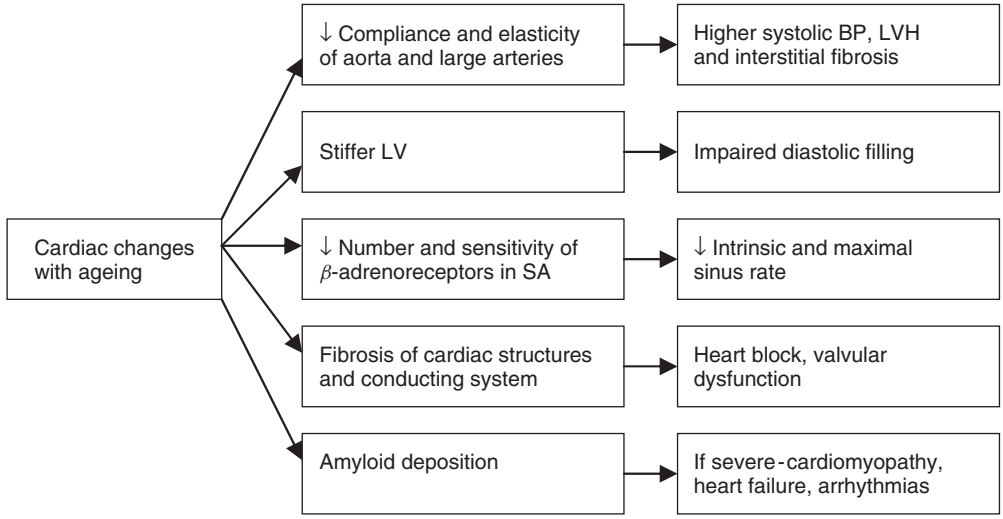

Figure 35.1 Changes in cardiovascular system with healthy ageing.

reports of partial reversal of age-associated changes with interventions such as exercise lends further credence to this hypothesis.[8,9]

Microscopic changes in the ageing heart are well described and include a decrease in number of myocytes with hypertrophy of remaining cells. Convincing mechanistic explanations for these changes are lacking although tissue hypoxia secondary to reduced capillary density has been postulated.[10] Contrary to previous belief, adult myocardial cells remain capable of active division and this has been demonstrated *in vitro* in response to myocardial injury.[11] There is an age-associated increase in other cardiac cell types and materials including interstitial fat, lipofuscin pigment and fibroblast numbers (and activity).[11] The magnitude and functional importance of cardiac interstitial fibrosis is debated[12] but age-related valvular fibrosis and calcification is common. The latter often causes valvular regurgitation or stenotic gradients, manifest on echocardiography or clinically as murmurs on auscultation. Previously thought to be benign, 'senile aortic sclerosis' is now recognized to be associated with significant increases in cardiovascular and total mortality.[13]

Intracellular deposits of amyloid are common in the older heart. Distinct patterns of atrial appendage amyloid and more generalized deposition are recognized.[14] In post-mortem studies amyloid deposits have been found in the majority of aged hearts with the highest prevalence (80–100%) reported in Japanese populations.[15] Although most elderly patients do not have symptoms from cardiac amyloid, some will develop extensive infiltration resulting in a clinical cardiomyopathy that can in turn be associated with heart failure and arrhythmias.[15] The electrocardiograph (ECG) may show low voltage complexes and on echocardiography, the myocardium has a characteristic bright 'speckling' appearance with other features of a restrictive physiology. In advanced cases virtually every cardiac structure can be infiltrated. Age-related reduction in the number of functional pacemaker cells in the sinoatrial node and myocyte cells in specialized conducting tissues are well described and are clinically manifest by ECG changes and predisposition to dysrhythmias such as 'sick sinus syndrome'.[16]

Biochemical changes with age have been reported including alterations in sarcoplasmic reticulum and Ca^{2+} uptake across membranes. In isolated senescent cardiac tissue slower myosin isoenzymes and decreased adenosine triphosphatase activity are also described.[17] These biochemical alterations result in prolongation of isovolumetric relaxation. These changes may be of functional importance, particularly with regard to reduced diastolic function and cardiac failure with preserved ejection fraction.

Changes in cardiac physiology with ageing

Healthy ageing is associated with little change in systolic function or cardiac output at rest. However, age-related changes in diastolic function are apparent on echocardiography or cardiac MRI.[18] There are progressive changes in the pattern of left ventricular filling, with numerous indirect measures of diastolic function showing deterioration with advancing age; the early phase of diastolic ventricular filling is delayed and maximal flow rate across the mitral valve is reduced; as a result a much greater proportion of ventricular filling occurs late in diastole during atrial contraction. These changes in diastolic function seem to be largely independent of disease. However, their precise aetiology and

in particular the role of reduced left ventricular compliance and myocardial relaxation patterns remains to be definitively established.[2,19] For most older people these changes are not of major consequence. However, the development of atrial fibrillation (AF) (and loss of the late ventricular filling phase) has much more severe adverse consequences in the older heart, with greatly reduced cardiac homeostatic reserve and maximum aerobic exercise capacity.

There is an age-related reduction in cardiac responsiveness to adrenergic stimuli, resulting in a decrease in both intrinsic and maximal sinus heart rate.[20] During exercise or other stressful stimuli, the increase in heart rate is attenuated in older people; at any given submaximal work-rate the heart rate rise is reduced and the older heart relies on dilatation and increased stroke volume to increase cardiac output (working on the physiological principles of the Starling curve). This compensatory response is effective at low or moderate workloads; however, cardiac reserve is reduced, with a reduction in maximal cardiac output in the older heart. These changes appear to be due to a reduction in both the number and sensitivity of cardiac β-receptors; the age-related changes described are akin to the effects of pharmacological β-blockade.

Arterial baroreceptors responses are slowed with increasing age. As a result, aged individuals typically exhibit increased arterial pressure variability with decreased cardiac heart rate variability and responsiveness.[21] It has been postulated that these changes predispose to postural hypotension and syncope in the elderly.

It could be argued that discussion of intrinsic ageing and the disease-free heart is a somewhat academic exercise. The reality is that most older people, at least in the developed world, have clinically relevant ischaemic cardiac disease. Atherosclerosis begins in adolescence and the incidence and prevalence of ischaemic heart disease increase dramatically with age.[22] Up to 30% of the over 65s have symptoms of ischaemic heart disease with angina or previous acute myocardial infarction. However, it has been estimated that a further 30% have clinically significant but covert or unrecognized disease. A variety of factors contribute to this hidden burden of disease. There may be barriers to communication or reporting such as chronic cognitive impairment. Symptoms may be masked by comorbidities that reduce exercise capacity, or cause other more clinically obvious symptoms. In addition ageing is associated with impaired perception of ischaemic cardiac pain; on exercise there is a delay from onset of myocardial ischaemia to symptoms of angina in older people. As a result when cardiac symptoms occur they may be vague or atypical.[23] Myocardial infarction may present as a confusional state or 'collapse', while myocardial ischaemia may provoke non-specific lethargy and reduced physical capacity. Therefore, ischaemic heart disease is a common cause of reduced cardiac homeostatic reserve in older people and in the event of a physiological stressor such as systemic illness, adverse clinical consequences such as myocardial ischaemia, heart failure or cardiac arrhythmias can readily occur. The presentation, diagnosis, and treatment of coronary artery disease in older people are discussed in detail in Chapter 37, Ischaemic heart disease.

Cardiac manifestations of non-cardiac disease

The brain

Cerebrovascular disease

Acute strokes in older people, including infarction, subarachnoid and intracranial haemorrhage are often associated with cardiac rhythm or conduction disturbances, and the 12-lead ECG may show repolarization patterns resembling acute myocardial infarction. Elevation in serum cardiac enzymes, particularly troponin, is seen in approximately 20% of patients with acute stroke and is associated with ECG changes and increased mortality. Although some patients will have underlying coronary thrombosis, these ECG and biomarker changes can occur in the absence of significant coronary arterial disease.[24] In this situation the underlying process may be a stress response with activation of the sympathoadrenal system causing patchy focal myocardial damage known as myocytolysis.[25]

Many older subjects with ischaemic cerebrovascular disease have comorbid coronary artery disease. Cardiac disease is the commonest cause of death in the first months following ischaemic stroke, with 2–6% of patients dying from cardiac causes. Risk is highest in the first days immediately post-ictus. Predictors include diabetes, LV dysfunction, renal impairment, long QTc and severe neurological impairment.[26]

Dementia and cognitive decline

Increasingly it is recognized that vascular disease is an important and potentially preventable contributor to dementia and cognitive decline in later life. Post-mortem studies have shown that Alzheimer's pathology on its own is often not sufficient to cause major cognitive decline. However, the combination of Alzheimer's pathology and ischaemic cerebrovascular disease (particularly small vessel ischaemia) carries particular risk of dementia.[27] Longitudinal population studies have shown that vascular risk factors, particularly hypertension, diabetes mellitus and cigarette smoking, are associated with increased risk of dementia.[28,29] Congestive cardiac failure (CCF) may also contribute to late-life cognitive impairment. Dementia is over-represented in CCF patients; predictors include left ventricular systolic dysfunction and arterial blood pressures below 130 mmHg.[30] A variety of mechanisms have been proposed including occult cerebral infarction,

low-grade small vessel ischaemia, activated thrombosis and blood pressure variability and altered cerebrovascular reactivity. A degree of cognitive dysfunction occurs in most older patients after cardiac surgery including coronary artery bypass grafting.[31] Those with pre-existing small vessel cerebral ischaemia are at particular risk. Low blood pressure during surgery and small cerebral embolic events are thought to be the main contributors.

The respiratory system

Cardiac failure and atrial fibrillation (AF) are common complications of serious respiratory illness in older people. Chronic obstructive pulmonary disease and reduced lung function (FEV1, forced expiratory volume) are independent risk factors for arrhythmias including AF. Respiratory infections such as influenza and respiratory syncytial virus are associated with increased risk of hospitalization for heart failure and sudden death.[32] Potential mechanisms include infection-induced rises in cytokines that have negative cardiac inotropic effects, and sympathetic nervous system activation.

While there is a considerable body of research focusing on the ageing left ventricle and aorta, age-associated changes in the right heart and pulmonary circulation are less well described. Population-based studies have suggested modest increases in pulmonary systolic pressure independent of respiratory disease; greater pulmonary pressures are associated with increased risk of cardiovascular events and mortality.[33]

Gastrointestinal system

Age is an independent risk factor for circulatory collapse and death after acute gastrointestinal haemorrhage. This is likely to be due to reduced homeostatic cardiac reserve.[34] Circulatory problems to the bowel are fortunately uncommon; however, the incidence does rise markedly with increasing age. Potential mechanisms include atherosclerosis of mesenteric arteries or cardio-embolism, particularly in AF. Symptoms are usually of pain, altered bowel habit and haematochezia although clinical presentation can range from mild transient symptoms to fulminant acute abdomen with gangrenous bowel.[35] For milder cases a conservative approach is often recommended with pharmacological treatment of underlying vascular risk factors. Older age is a predictor of poor outcome.[36]

Exposure to helicobacter pylori infection becomes increasingly common with advancing age. In young subjects it has been suggested that helicobacter may be a contributory cause of ischaemic heart disease, in association with raised fibrinogen levels. However, no convincing link has been confirmed with ischaemic heart disease in elderly subjects; observational studies claiming that helicobacter eradication therapy decreases fibrinogen levels in coronary heart disease are likely to be confounded by regression to the mean.[37]

The association of aortic valvular disease (particularly aortic stenosis) with gastrointestinal angiodysplasia, the 'Heyde Syndrome' has been recognized for many years. However, the nature and strength of the link has been debated as both conditions are relatively common, particularly in older age. A biological mechanism for this association involving activation of clotting factors has been postulated.[38]

Renal system

Deterioration in renal and cardiac function often occurs together in older people. Renal impairment in older people is associated with increased risk of ischaemic cardiovascular disease. The risk is inversely related to glomerular filtration rate and is significantly increased by the time biochemical alterations in serum creatinine are apparent.[39] This association is partly due to common aetiologies, including hypertension and atherosclerosis.

A cardio-renal 'vicious circle' is well recognized in older patients wherein impaired natriuretic ability of the ageing nephron results in fluid overload and CCF, while the older, diseased heart is unable to maintain adequate cardiac output and perfusion pressure to the kidneys leading to further deterioration in renal function. When elderly patients with chronic heart failure develop impaired renal function, this is an adverse prognostic factor for hospitalization and death.

Cardiovascular disease remains the leading cause of death in patients with end-stage renal disease, accounting for around half of all deaths. The risk remains elevated even after renal transplantation.[40] An association between renal impairment and modest increases in serum levels of cardiac biomarkers such as troponin has also been reported. Studies detailing the cardiac phenotype of patients with end-stage renal failure and raised troponin have shown increased incidence of cardiac risk factors and LV impairment but no excess of coronary artery disease or demonstrable ischaemic damage.[41,42] Nonetheless, elevated troponin in renal failure is associated with increased cardiovascular risk.[41]

Endocrine abnormalities and the cardiovascular system

Thyroid

Hyperthyroidism is common in older people, with cardiovascular manifestations dominating the clinical presentation; palpitations, dyspnoea, sinus tachycardia, arrhythmias, and systolic hypertension are common features. Heart failure is particularly likely if pre-existing heart disease is present. The risk of AF (paroxysmal or

chronic) is increased in older patients. In the absence of underlying heart disease, AF may revert to sinus rhythm when a euthyroid state is achieved. However, in older patients or when AF has been present for a long duration, the rate of reversion is lower.[43] Cardiovascular complications remain the principle cause of death, even after treatment of hyperthyroidism.

Hypothyroidism also has important cardiac manifestations in older people. Bradycardia, non-pitting peripheral oedema, pericardial effusion, CCF and low-voltage complexes on ECG are all recognized.[43] Exertional dyspnoea and easy fatigability are common complaints, resulting from a combination of systolic and diastolic dysfunction on effort.[44] Endothelial dysfunction may increase the risk of hypertension and arterial thrombotic events and there is increased risk of atherosclerosis due to hypertension and atherogenic lipid profile. Decreased metabolic demand on the myocardium and low physical activity levels in hypothyroidism make symptoms of angina less frequent even in the presence of significant coronary artery disease. Many of these cardiac manifestations of hypothyroidism reverse with thyroxine replacement therapy. However, it is recommended that extra caution is exercized in the elderly while initiating treatment to avoid precipitating acute myocardial infarction and heart failure, as they are likely to have underlying ischaemic heart disease. The initial dose of thyroxine should normally be ~25% of the anticipated replacement dose, increased in a stepwise fashion at 6–8 week intervals.[45]

Subclinical thyroid dysfunction is common in older patients, with a prevalence of asymptomatic (biochemical) hypothyroidism of ~10% and hyperthyroidism in 1.5%. These laboratory endocrine abnormalities are associated with detrimental cardiovascular effects; prospective longitudinal studies have shown that subclinical hypothyroidism, with thyroid stimulating hormone (TSH) levels greater than $10\,mU\,l^{-1}$, is associated with increased incidence of heart failure.[46] Subclinical hyperthyroidism (with low serum TSH levels) is associated with approximately two- to threefold increase risk of developing AF.[47,48] In this context this arrhythmia may be a more benign phenomenon than in primary cardiac disease.[47] However, there is some evidence that low TSH is associated with increased cardiovascular morbidity and mortality.[49] Thyroid hormones have positive inotropic and chronotropic effects and cardiac benefits for hypothyroid subjects from hormone replacement would seem likely; this is supported by imaging studies which have suggested reversal of cardiac dysfunction in patients rendered biochemically euthyroid.[50] However, no adequately powered randomized controlled trials using cardiac endpoints are available.[51] It is not certain that active treatment of subclinical hypo- or hyperthyroidism to achieve a euthyroid state prevents cardiac complications.

Other hormones

Acromegaly and associated growth hormone excess is associated with cardiac enlargement and hypertension. Chronic overproduction of growth hormone also impairs carbohydrate metabolism and leads to a state of hyperinsulinaemia and insulin resistance with consequent increased risk of diabetes mellitus. Elderly people with acromegaly are more likely to develop acromegalic cardiomyopathy with cardiac enlargement and chronic heart failure that is often refractory to treatment. Older patients with hypopituitarism and low serum levels of growth hormone also appear to be at risk of cardiac complications, including acute myocardial infarction. Growth hormone replacement therapy may ameliorate this risk.[52]

The potential link of low levels of sex hormones with cardiovascular disease has attracted considerable attention. Despite apparent beneficial effects on traditional vascular risk factors, prospective studies have shown that estrogen replacement in post-menopausal women is associated with increased incidence of vascular events.[53] In males, low serum testosterone has also been associated with cardiovascular risk factors but definitive evidence of a beneficial cardiac effect of replacement is lacking.[54]

Diabetes mellitus (see Chapter 101, Diabetes mellitus)

A high index of suspicion is necessary for detection of myocardial ischaemia in the elderly with diabetes mellitus as they are more likely to have silent or atypical disease, particularly in females. The reported incidence of arteriosclerotic coronary heart disease in older diabetic patients is likely to be an underestimate as most studies have excluded the elderly with renal dysfunction or other comorbidities.[55] Elderly diabetics are more likely to have multivessel coronary artery disease (often unsuitable for percutaneous revascularization procedures or coronary artery bypass grafting), and have an increased risk of CCF. Diabetes is also associated with LVH independent of other common risk factors.[56] In addition, diabetic cardiomyopathy associated with small vessel disease has been described.

Metabolic syndrome

The concept of the metabolic syndrome was developed to improve understanding of links between insulin resistance and vascular disease. The components of this prediabetic state include raised BMI, elevated triglycerides and blood sugar, low high-density lipoprotein, and hypertension. However, it appears that diagnosis of the metabolic syndrome carries limited clinical utility in older age; while it is associated with increased risk of type-2 diabetes it

has weak or no associations with vascular risk in elderly populations.[57]

Systemic infections and the heart

A variety of acute and chronic systemic infections have been suggested to increase the risk of acute ischaemic vascular events. Even minor acute infections are associated with myocardial infarction and stroke. Although various specific infective agents have been implicated, the process seems most likely to be a generic systemic response to any viral or bacterial infection.[58] Factors such as dehydration, immobility and increased blood coaguability are likely to be responsible. The evidence for a strong causal link between chronic infection and vascular disease is less compelling.[59] There is a modest association between periodontal disease and risk of ischaemic vascular events (including acute myocardial infarction and stroke); the mechanism could involve systemic inflammation contributing to atherosclerosis and thrombosis. However, absence of a standard definition for periodontal disease complicates interpretation of results. In addition there are multiple potential confounding risk factors common to both conditions. Additional large-scale longitudinal epidemiologic and intervention studies are necessary to validate this association and to determine causality.[60]

Cancer

Cardiac neoplasms may be primary or metastatic and although rare, as with most solid organs tumours, an age-related association is apparent. Autopsy series have found that the majority of cardiac tumours are due to secondary spread from primary neoplasms in lung, breast or from haematological malignancy.[61] Primary cardiac myxomas may present with cardiac symptoms or neurological manifestations particularly ischaemic stroke.[62]

Nutrition and cardiovascular system in the elderly

Symptomatic heart failure, especially in the elderly, can affect food intake, leading to malnourishment. A syndrome of cardiac cachexia is recognized and is associated with poor outcomes, independent of severity of heart failure. The weight loss seen in these patients is greater than would be expected from poor diet alone and metabolic, neurohormonal and immune abnormalities may play a role.[63] Besides presenting with significantly more comorbidity, patients with low BMI are at higher risk of postoperative complications following cardiac surgery.[64]

Conclusions

Cardiac manifestations of systemic disease are common in older people. Healthy ageing is associated with a reduction in cardiac homeostatic reserve, increasing the risk of cardiac arrhythmias and heart failure with many non-cardiac illnesses. In addition clinically significant ischaemic heart disease is present in the majority of over 65s in the developed world, further reducing cardiac reserve, and increasing the risk of myocardial ischaemia in response to almost any severe systemic non-cardiac disease. Ischaemic heart disease is linked to dysfunction in numerous other organ systems, and the classic scenario of multiple pathologies in an older person often includes cardiac disease. Optimal management of the older patient requires that the multiple interacting contributors to symptoms or functional decline are identified to allow key modifiable factors to be prevented or treated.

Key points

- Ageing is associated with a marked reduction in cardiac homeostatic reserve due to a combination of intrinsic ageing, and a high prevalence of underlying cardiac disease (particularly ischaemic heart disease).
- This reduced homeostatic reserve greatly increases the risk of cardiac dysfunction (including heart failure and arrhythmias) with non-cardiac disease in older people.
- Cardiac dysfunction in older people also places other organ systems at risk. Examples include increased risk of dementia with both atrial fibrillation and chronic heart failure.
- Frequently there is a complex interaction between different organ systems. For example deterioration in renal and cardiac functions often occur together in older people.
- Optimal management of the older patient requires that these multiple interacting contributors to symptoms or functional decline are recognized, and key modifiable contributors prevented or treated.

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CHAPTER 36

Arrhythmias

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The population is ageing and, as the heart ages, pathophysiological changes occur that predispose to numerous rhythm disturbances. Prognostic improvements made in the management of heart disease have further increased the burden by prolonging exposure to conditions that promote the development of arrhythmias. Arrhythmias are associated with a substantial risk of morbidity and mortality and the management of arrhythmias in the elderly presents important challenges. Clinical presentation can vary from one extreme (asymptomatic incidental finding) to the other (acute haemodynamic collapse) and includes a myriad of non-specific symptoms common to many disorders. The general principles of arrhythmia management in the elderly are the same as with other ages, but plans must be individualized as there is a vast scope amongst the elderly for comorbidity, polypharmacy, impaired cognition, poor exercise tolerance and other factors that modify the risk–benefit ratio. This chapter reviews arrhythmias in the elderly and their associated morbidity and mortality, with increased emphasis on the commonest rhythm disorder, atrial fibrillation.

The elderly heart

Ageing of the heart is associated with the deposition of amyloid in the atrial myocardium, a gradual loss of the specialized pacemaker myocytes of the sinoatrial (SA) node and the deposition of collagen and fibrous tissue in the specialized ventricular conduction tissue. These ageing processes are associated with a pathological outcome in some patients. For instance, loss of SA node pacemaker cells contributes to the development of sick sinus syndrome. This process is augmented by pathological changes secondary to cardiovascular disease such as hypertension and coronary atherosclerosis, both of which increase in incidence with age. In reviewing 12-lead and 24 h electrocardiogram (ECG) survey findings in the elderly, it can be difficult to distinguish between whether purely ageing or pathological processes are responsible.

12-Lead and ambulatory ECG surveys

Findings of a prolonged PR interval, left-axis deviation and bundle branch block (BBB) are more common in the elderly. First-degree heart block, as a lone finding in an asymptomatic patient, is not associated with an adverse prognosis. Left-axis deviation is associated with cardiovascular disease but in the absence of clinical disease does not carry a worse prognosis. Increases in left ventricular hypertrophy and left BBB with age correspond to the increased incidence of cardiovascular disease and clearly are associated with an increased mortality. Right BBB is more common than left in the elderly, but has no prognostic impact *per se*.

In the absence of medication, a sustained bradycardia is not a normal finding in the elderly. However, elderly subjects do show a significant reduction in 24 h heart rate variability.[1] A survey of 500 asymptomatic individuals aged 50–80 years[2] found no association between heart rate and age, and a study of 1372 individuals aged 65 years and older[3] found no association between bradycardia and age. Various studies have shown a small decline in mean heart rate with age,[4] but even in healthy subjects aged 80–99 years, mean heart rate is still >70 bpm.[1] A persistent and significant bradycardia should alert the clinician to the possibility of sinus node disease. There is a low incidence of sinus arrhythmia in the elderly, but ectopic activity is considerably increased. Specific brady- and tachyarrhythmias are discussed individually below.

Symptomatic bradycardias

Cardiac impulse originates in the SA node, propagates through the atria and is normally conducted to the ventricles via the atrioventricular (AV) node and bundle of His. Bradycardia can result from abnormalities at any level: dysfunction of SA node automaticity, conduction disturbances within the AV node or bundle of His. These are discussed individually below. Bundle branch or fascicular blocks may

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prolong ventricular depolarization (QRS complex width) or cause electrical axis deviation, but will not result in a bradycardia unless conduction through all fascicles is interrupted, equivalent to complete AV block. The autonomic nervous system regulates sinus node automaticity and AV nodal conduction. The balance of parasympathetic and sympathetic tone is subject to influence from a host of extrinsic factors: physiological [e.g. sleep (see Chapter 54, Sleep apnoea and sleep disorders)], pathological [e.g. hypothyroidism (see Chapter 98, Thyroid disorders)] and iatrogenic (e.g. medication). The causes of a bradycardia are summarized in Table 36.1.

Presentation

Episodes of bradycardia are common in all age groups. However, a sustained bradycardia is not a normal finding in the elderly and, as discussed above, implies pathology. The presence or absence of symptoms is principally determined by the heart's ability to compensate for a bradycardia. Cardiac output is the product of heart rate and left ventricular stroke volume. If the latter cannot increase sufficiently to match demand and peripheral and/or cerebral perfusion falls, this will result in symptoms. These vary from understated symptoms such as lack of concentration, fatigue, poor memory, dizziness and myalgia to more pressing concerns of syncope and heart failure.

Assessment

Documentation of a bradycardia (rhythm strip, 12-lead ECG or ambulatory monitoring) is not sufficient. The symptoms described above are all non-specific and differential diagnoses are extensive, especially in the elderly. It is essential to establish a correlation between the patient's symptoms and the occurrence of bradycardia, otherwise treatment of the arrhythmia may be successful (e.g. pacemaker implantation), but without any symptomatic benefit. History, examination and investigations should be targeted at confirming the presence of arrhythmia, its association with symptoms, to differentiate physiology from pathology and to recognize reversible risk factors (such as medication, hypothyroidism, sleep apnoea).

Sinus node dysfunction (sick sinus syndrome)

The term sick sinus syndrome confers the impression of a constellation of multiple electrocardiographic manifestations such as sinus bradycardia, inappropriate sinus node response to exercise (chronotropic incompetence), sinoatrial block and periods of sinus arrest, particularly occurring after paroxysms of atrial tachyarrhythmias ('tachybrady syndrome'). Dysfunction may progress to the stage that no sinus beats occur (Figure 36.1). Both paroxysmal and chronic atrial fibrillation are commonly associated with sinus node disease. Sinus node dysfunction is primarily

Table 36.1 Causes of bradycardia.

System	Cause
Cardiovascular	Ischaemia/infarction
	Infiltrative disorders (e.g. sarcoid, amyloid, haemochromatosis)
	Inflammatory disorders (e.g. systemic lupus erythaematosus, rheumatoid)
Respiratory	Obstructive sleep apnoea
Medication	β-Blockers (including topical eye preparations)
	Anti-arrhythmics (e.g. digoxin, amiodarone)
	Antihypertensives (e.g. calcium channel antagonists)
Iatrogenic	Valve replacement
	Catheter/surgical ablation
	Correction of congenital heart disease
Endocrine	Hypokalaemia
	Hyperkalaemia
	Hypothyroidism
Neurological	Raised intracranial pressure
	Increased vagal tone (e.g. micturition, defecation, coughing)
	Carotid sinus hypersensitivity
Infectious disease	Infective endocarditis
	Lyme disease
	Chagas disease
Miscellaneous	Hypothermia
	Metastatic disease

SLE, systemic lupus erythaematosus.

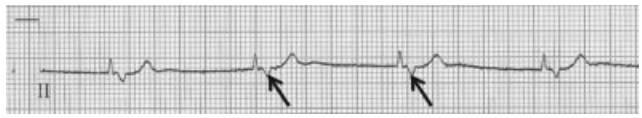

Figure 36.1 Junctional bradycardia: failure of sinus beats has resulted in a junctional escape rhythm. The junctional impulses are seen conducting antegradely causing ventricular depolarization, but also retrogradely into the atria causing inverted P waves, seen immediately after the QRS complex (arrows).

a disease of the elderly resulting from degenerative or ischaemic causes which may also affect other conductive tissue including the AV node. The majority of patients experience recurrent syncope from sinus pauses with inadequate escape rhythm or marked sinus bradycardia. Mortality appears to be unaffected by sinus node dysfunction[5] and survival is influenced by associated pathology such as ischaemic heart disease.

The main indications for pacing in sinus node dysfunction are as follows:[6]

- Sinus node dysfunction with documented symptomatic bradycardia, symptomatic chronotropic incompetence or where bradycardia is the result of medication necessary to treat other medical conditions, such as in the treatment of tachyarrhythmias (class I recommendation).
- Sinus node dysfunction and heart rate <40 bpm, where an association between symptoms consistent with bradycardia and the presence of bradycardia has not been clearly established; syncope of unknown origin in presence of significant sinus node abnormalities on electrophysiological testing (class IIa recommendations).

Atrioventricular blocks

First-degree heart block

The PR interval (time from onset of P wave to onset of QRS complex) corresponds to the time from initiation of atrial depolarization, conduction through the atria and into the bundle branch system via the AV node and bundle of His. A prolonged PR interval (>0.2 s) with preservation of 1:1 AV conduction is termed *first-degree heart block*. The incidence of first-degree AV block increases with ageing. Moderate prolongation of the PR interval in this fashion is a benign condition,[7] but PR intervals >0.3 s can be symptomatic.[8] Marked first-degree AV block could cause loss of synchrony between the atria and the ventricles leading to incomplete atrial and ventricular filling and increased capillary wedge pressure.

Indications for pacing in first-degree AV block are as follows:[6]

- First-degree heart block associated with symptoms of a delay in AV synchronous contraction or haemodynamic compromise (class IIa recommendation).
- First-degree heart block in association with neuromuscular diseases due to unpredictable progression of AV disease; drug-related AV block where the block is expected to persist even after withdrawal of the drug (class IIb recommendation).

Second-degree heart block

This is an intermittent failure of atrial depolarization to result in ventricular depolarization and tends to occur in various patterns. Mobitz type I second-degree heart block (Wenckebach) is present when there is progressive lengthening of the PR interval with each beat until an atrial depolarization is not conducted, resulting in a dropped beat. The PR interval resets and the cycle resumes. Mobitz type II second-degree heart block occurs when atrial depolarizations are intermittently blocked without preceding progressive PR interval prolongation. AV conduction occurring in a 2:1 fashion (or higher) represents another pattern of second-degree heart block. If block of two or more consecutive P waves occurs, this is termed *advanced second-degree heart block* (see Figure 36.2).

Indications for pacing in second-degree AV block are as follows:[6]

- Any form of second-degree heart block associated with symptomatic bradycardia or ventricular arrhythmias presumed to be secondary to the AV block (class I recommendation).
- Advanced second-degree AV block in symptom-free patients with documented significant periods of pauses or asystole lasting ≥3.0 s or any escape rhythm of rate <40 bpm in an awake patient (class I recommendation).
- Advanced second-degree AV block associated with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia (class I recommendation).
- Unresolving advanced second-degree block following cardiac surgery or catheter ablation of AV junction (class I recommendation).
- AV block during exercise in the absence of myocardial ischaemia.
- Type II second-degree heart block with a wide QRS complex (class I recommendation).
- Asymptomatic type II second-degree heart block with narrow QRS complex (class IIa recommendation).

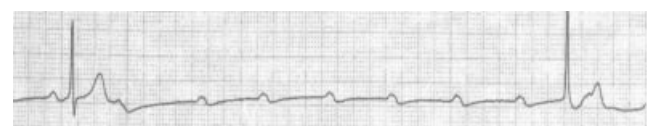

Figure 36.2 Rhythm strip showing advanced second-degree heart block. The second ventricular complex is a junctional escape beat.

• Associated with symptoms of a delay in AV synchronous contraction or haemodynamic compromise (class IIa recommendation).
• In association with neuromuscular diseases due to unpredictable progression of AV disease; drug-related AV block where the block is expected to persist even after withdrawal of the drug (class IIb recommendation).

Third-degree heart block (complete heart block)

Third-degree heart block is a complete block of conduction between the atria and ventricles resulting in regular atrial activity and the presence of an independent escape rhythm. The escape rhythm is generally ventricular in origin with a wide QRS complex and rate of ~30–40 bpm. Nodal or junctional escape rhythms imply that the anatomical level of block is higher within the AV node or the bundle of His (Figure 36.3). The lower the origin of the escape rhythm, the less specialized and hence less reliable is the conduction tissue.

Indications for pacing in complete AV block are as follows:[6]

• Third-degree heart block with one of the following features: symptomatic bradycardia; documented asystole ≥3.0 s or any escape rhythm of rate <40 bpm in symptom-free awake patients; unresolving block following cardiac surgery or catheter ablation of AV junction; asymptomatic third-degree heart block, especially in the context of LV dysfunction or cardiomegaly; AV block during exercise in the absence of myocardial ischaemia (class I recommendations).
• Asymptomatic heart block in the absence of cardiomegaly (class IIa recommendation).
• Drug-related AV block where the block is expected to persist even after withdrawal of the drug (class IIb recommendation).

Choice of pacemaker

Once the decision to implant a pacemaker has been made, consideration should be given to the appropriate pacemaker mode. The choice lies between single-chamber ventricular-only pacing (VVI/R), dual chamber atrial plus ventricular pacing (DDD/R) or single-chamber atrial-only pacing (AAI/R). DDD or AAI pacing allow the preservation of normal physiology by maintaining AV synchrony. Single-chamber AAI pacing is indicated in patients with pure sinus node disease with no evidence of either existing or future development of disease elsewhere in the conduction system. However, elderly patients, who may initially present with apparently pure sinus node dysfunction, have a greater likelihood of more widespread conduction system involvement and therefore generally will not benefit from atrial-only pacing. Physiological pacing may improve haemodynamics, but dual-chamber systems can be technically more challenging as two leads are required with greater potential for late complications. A series of large prospective, randomized trials have compared ventricular pacing (VVI/R) with physiological systems (DDD/R or AAI/R) for sinus node dysfunction or AV block (see Table 36.2 for a summary of these trials). A key limitation of these trials is that a significant number of patients either crossed over between treatment arms or dropped out of their assigned pacing mode. Meta-analysis of these five trials shows that there is no difference in overall mortality between ventricular and physiological pacing systems and no difference in new-onset heart failure or improvement or progression of any existing heart failure.[9]

However, a statistically significant reduction in the development of AF was found with physiological pacing, particularly in the Mode Selection Trial (MOST) and Canadian Trial Of Physiological Pacing (CTOPP) trial. There was borderline reduction in thromboembolic stroke with physiological pacing. Some cross-over studies with intra-patient comparison between the two pacing modes have shown improved functional capacity and increased patient preference for dual-chamber pacing.[10]

Therefore, elderly patients with sinus node dysfunction who require pacing should be considered for a dual chamber system. No clear evidence exists for benefit of dual-chamber pacing over simple ventricular pacing for AV block in the elderly, but given the overall findings from trials, physiological pacing should be considered for those likely to be pacemaker dependent. Active elderly patients over 70 years of age appear to benefit from DDD pacing in terms of improvement in quality of life.[11] However, the final decision in the elderly depends on an individual basis after taking into account patient preferences, co-morbidities and the available resources.

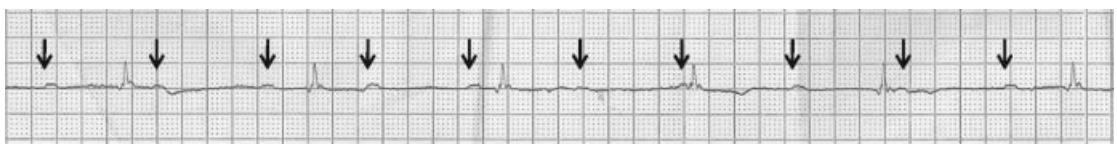

Figure 36.3 Complete heart block. Rhythm strip showing P waves (arrows) that are independent and unrelated to QRS complexes. The QRS complexes are relatively narrow, suggestive of junctional escape rhythm.

Table 36.2 Characteristics of trials comparing ventricular and physiological pacing.

Trial[a]	*n*	Age (years)	Indication[a]	Follow-up (years)	Results
CTOPP	2568	73	SND or AVB	3.1	No significant difference in stroke, cardiovascular death or hospitalization for heart failure Annual rate of AF significantly lower in physiological group, but higher perioperative complication rate
CTOPP (long-term)	2568	73	SND or AVB	6	No significant difference in cardiovascular death, stroke or total mortality Persistent significantly lower rate of AF in physiological group
MOST	2010	74 (median)	SND	2.8	No significant difference in death, non-fatal stroke or hospitalization for heart failure Incidence of AF significantly lower in physiological group
PASE	407	76	SND or AVB	2.5	No significant difference in stroke, stroke or all-cause mortality, stroke, death or hospitalization for heart failure No significant difference in the development of AF
UKPACE	2021	80	AVB	4.6	No significant difference in all-cause mortality No significant difference in secondary end-points of AF or heart failure

[a]CTOPP, Canadian Trial Of Physiologic Pacing:[13] CTOPP (long-term), Canadian Trial Of Physiologic Pacing long-term follow-up:[14] MOST, Mode Selection Trial:[15] PASE, pacemaker selection in the elderly:[16] UKPACE, United Kingdom Pacing and Cardiovascular Events; SND, sinus node dysfunction: AVB, atrioventricular block.

Complications of pacemaker implantation

Complications can occur during implantation and include pneumothorax (1–2% with subclavian vein approach; <0.1% with cephalic or axillary vein approach), bleeding, myocardial perforation and tamponade (<0.2%), lead dislodgement and failure to sense or capture. Post-procedure complications are bruising, wound haematoma, infection (<1%), device erosion, lead fracture and box or lead dislodgement. In a recent series, early complications (within 2 weeks of implantation) occurred in 6.7% of patients and late complications in 7.2% of patients.[12] The majority of these patients required an invasive correction of the complication. Despite the reduction in size of the modern pacemaker, special considerations have to be made for elderly patients. Devices are generally implanted subcutaneously between the skin and the pectoral muscle in the infra-clavicular region, but skeletal deformities resulting from osteoarthritis or osteoporosis of the shoulder, spine or pectoral region may occasionally prevent this. In addition, wound healing and device erosion through the skin are more likely to occur with cachexia and thinning skin. In such patients, the pacemaker may be better positioned under the pectoral muscle. Clearly, as with any procedure, a risk–benefit assessment has to be made on an individual basis.

Atrial tachyarrhythmias

Atrial ectopic beats

These are a common finding in the elderly and, if frequent, can result in a pulse that could be confused with AF. No specific treatment is required, but if symptomatic, patients generally respond to β-blocker therapy.

Atrial tachycardia

Short bursts of atrial tachycardia are common in the elderly (Figure 36.4). In many cases, no symptoms are associated and no treatment may be needed. Sometimes the atrial tachycardia triggers AF or causes rapid ventricular rates when treatment of the tachycardia may become necessary. Most elderly patients will achieve symptomatic benefit from β-blocker therapy, and some may require anti-arrhythmic medication (e.g. amiodarone, sotalol) or urgent direct current cardioversion (DCC) if haemodynamically unstable. Percutaneous catheter ablation utilizing radiofrequency or cryo energy is increasingly used, but success rates are generally higher in younger patients and therefore not currently a preferred option in the elderly.

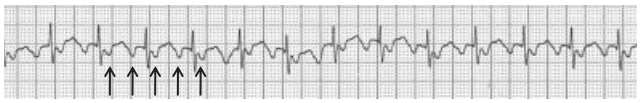

Figure 36.4 Atrial tachycardia. Abnormal, inverted P waves are seen (arrows) with 2:1 conduction to the ventricles. The tracing may appear like atrial flutter, but note that the P wave rate or cycle length is less than the typical flutter cycle length of 300 bpm.

Multifocal atrial tachycardia (MAT)

Another common atrial arrhythmia in the elderly, multifocal atrial tachycardia (MAT), is characterized by the appearance of diverse P wave morphologies as complexes originate from different foci within the atria. This can result in irregular R–R intervals and hence clinically mimic AF. There is an association with chronic airways disease and drug toxicity (digoxin, theophyllines and tricyclic antidepressants). Treatment should be aimed at the underlying cause.

Atrial flutter

Atrial flutter and AF are two ends of the same spectrum. Whereas the atria are activated in a chaotic manner in AF, atrial flutter consists of organized atrial activation seen on the ECG as a regular saw-tooth pattern of flutter waves with typically a flutter-wave rate of ~300 bpm (see Figure 36.5). A physiological 2:1 AV block frequently occurs and atrial flutter should always be suspected when a patients with a ventricular rate of 150 bpm. In the elderly, variable 4:1, 8:1 or other AV ratios may also be seen. Vagal manoeuvres or intravenous adenosine can temporarily increase the AV block, making flutter waves more visible. With typical (counterclockwise) atrial flutter, flutter waves are seen inverted in the inferior limb leads, giving rise to the characteristic saw-tooth appearance on the ECG. Atrial flutter commonly occurs in patients with AF and vice versa. Antiarrhythmic medication prescribed for AF can convert the AF into atrial flutter. Management of the two conditions is essentially similar and although the stroke risk associated with atrial flutter may not be as high as for AF, there is still a substantial risk[17] and a high likelihood of coexisting AF requiring the use of anticoagulation. In a given elderly patient, unlike other atrial arrhythmias, catheter ablation of typical atrial flutter may be performed with relative ease and high curative rates.

Atrial fibrillation

AF is characterized by disorganized atrial activity confirmed on the ECG by the substitution of regular P-wave activity by rapid fibrillatory waves varying in shape, amplitude and timing. If AV node conduction is intact,

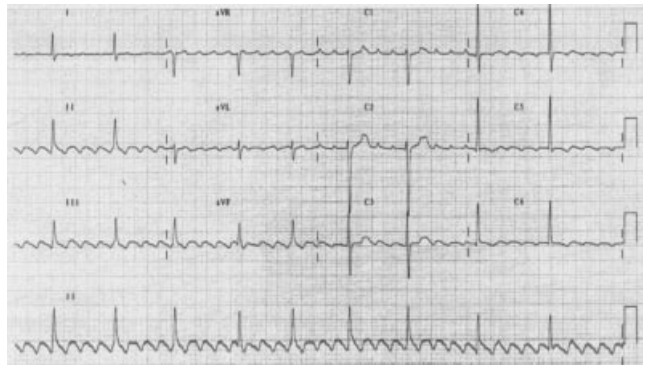

Figure 36.5 12-Lead ECG of typical atrial flutter with variable AV block. Note the inverted P waves (flutter waves) in the inferior leads II, III and aVF. The flutter wave cycle length is 300 bpm.

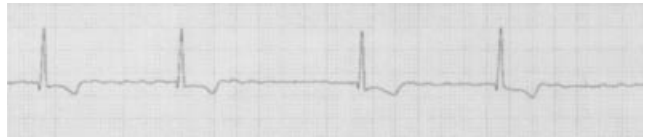

Figure 36.6 Rhythm strip of patient in AF with a slow ventricular response.

Figure 36.7 Lead II rhythm strip of a patient with chronic AF who presented with syncope. The rhythm is regular with fibrillatory baseline and absence of P waves, suggestive of complete heart block in the setting of AF.

the chaotic atrial activation will result in a rapid and irregular ventricular response. In the elderly, AV conduction may be impaired. A slower ventricular rate is common and sometimes verges on a symptomatic bradycardia (see Figure 36.6). The presence of regular rhythm on the ECG with a fibrillatory baseline implies development of complete AV block in a patient with AF, the regularity arising from the escape rhythm (Figure 36.7).

Classification

AF can be classified into five types based on the presentation, duration and choice of treatment strategy. When the first episode is detected, it is important to understand that its duration may be uncertain and there may have been previous episodes, which were not symptomatic, remembered or documented. After first detection, AF is then subclassified into the following categories according to its time course and intervention: *paroxysmal (PAF), persistent, long-standing persistent* and *permanent* atrial fibrillation. PAF is characterized by recurrent episodes of AF alternating with

sinus rhythm. The characteristic feature of PAF is that the episodes terminate spontaneously, usually within 48 h. If the episodes of fibrillation continue for more than 7 days or patients require intervention to restore sinus rhythm, this is termed persistent AF. When AF has lasted for ≥1 year and when it is decided to adopt a rhythm-control strategy, AF is termed long-standing persistent AF. Permanent AF is more a statement of intent rather than a duration or pathological based description and is reserved for patients in whom AF is resistant to conversion or accepted for rate control by the patient and there are no further attempts to achieve sinus rhythm. Permanent AF is redesignated long-standing persistent AF if there is a change of plan towards adopting a rhythm-control strategy.[18]

Epidemiology

AF affects 1–2% of the general population and is the commonest sustained arrhythmia in the elderly. The true prevalence of AF may be closer to 2% as many patients remain asymptomatic and may never present to a hospital. The prevalence of AF increases with age from <0.5% at 40–50 years to 5–15% at 80 years.[19]

Men are more often affected than women. An analysis of 1.4 million patients registered with 211 general practices in England and Wales showed that prevalence rates increased with age from <1 in 1000 in those under 35 years of age to >100 in 1000 in those aged 85 years and older.[20] The prevalence of AF is estimated to double in the next 50 years.[21]

We are in part a victim of our own success owing to prognostic improvements made in coronary heart disease and heart failure, conditions known to predispose to the development of AF. This, together with an ageing population, has led to the description of a near-epidemic of AF.[22] AF increases the risk of stroke fivefold. In 2000, the projected direct cost of AF to the UK National Health Service (NHS) was calculated at £459 million, 0.98% of total NHS expenditure,[23] a conservative estimate as costs related to stroke rehabilitation and anticoagulant-related haemorrhage were not considered.

Aetiology

Valvular AF

It is essential to make a distinction between valvular and non-valvular AF because of the consequence for stroke risk. Valvular heart disease is present in about 30% of patients with AF.[24]

Mitral stenosis and/or regurgitation, and in its later stages aortic stenosis, cause left atrial dilatation leading to AF. Rheumatic heart disease is now relatively rare in developed nations. In the Framingham Study, patients with rheumatic heart disease and AF had a 17-fold increase in stroke risk compared with age-matched controls.[25]

Non-valvular AF

AF occurring in the absence of rheumatic mitral stenosis or a prosthetic heart valve is termed *non-valvular AF*,[18] which can then be further subdivided as follows.

With associated cardiovascular disease

Hypertension (see Chapter 40, Hypertension), diabetes requiring medical treatment, heart failure (see Chapter 41, Heart failure), cardiomyopathies, coronary artery disease (Chapter 37, Ischaemic heart disease) and congenital heart defects such as atrial septal defect are commonly associated with AF. Of these, heart failure carries the highest predictive risk for the development of AF.[26] Hypertension is identified as a risk factor for AF and related complications such stroke and thromboembolism.

Hypertension, when associated with left ventricular hypertrophy by electrical criteria on the ECG, strengthens its contribution towards predicting development of AF. Coronary artery disease can be both a reversible risk factor (ongoing ischaemia or infarction) or irreversible (scar formation from prior infarction).

Other causes

Other identifiable and potentially reversible causes include obesity and obstructive sleep apnoea, electrolyte disturbance, sepsis, stress, hyperthyroidism, pulmonary disease, hypoxia and alcohol binge drinking. These factors need to be considered both in a first detected episode of AF and for the patient with a recent compromise in rate control.

Lone AF

Patients with a structurally normal heart in whom no identifiable cause can be found for their AF are denoted as having lone AF. This is probably rare in the elderly since almost all patients will have a degree of underlying heart disease by this stage and such a diagnosis of exclusion should only be made with caution in the elderly. In a small number of younger patients, sympathetic or vagal overstimulation may trigger AF and could influence the choice of anti-arrhythmic medication.

Consequences of AF

AF independently increases the mortality by twofold and is associated with stroke, other systemic thromboembolic disease, heart failure and related morbidity, leading to poor quality of life. Only antithrombotic treatment has been shown to reduce AF-related mortality.[27]

Atrial remodelling

It is a common finding for patients presenting with PAF to cardiovert spontaneously to sinus rhythm within 24 h of its onset.

The success of electrical or chemical cardioversion and the subsequent maintenance of sinus rhythm are generally higher with AF of a shorter duration. These observations are consistent with the concept that AF itself is capable of inducing an electrical remodelling of the atria, which in turn sustains the arrhythmia. Electrophysiological artificial maintenance of AF in animal models has been shown to induce reversible atrial changes (shortened atrial refractoriness) that lead to the perpetuation of AF[28] and eventually to histological (cellular dedifferentiation, fibrosis) and gross structural changes (atrial dilatation).

Haemodynamic function

With the chaotic activation inherent in AF, synchronous atrial mechanical function is not possible. The left ventricle in AF can only fill passively in the absence the late diastolic contribution from atrial contraction. This in turn can lead to a 5–15% decrease in cardiac output, an effect that is more pronounced in patients with reduced ventricular compliance (e.g. hypertensives) in whom ventricular filling is significantly reliant on the atrial contribution. Further deterioration in haemodynamic function results from high ventricular rates due to shortening of the diastolic filling time and additionally tachycardia-related myopathy (tachycardiomyopathy) at rates persistently above 120–130 bpm. Restoration of atrial mechanical function after successful ventricular rate control or cardioversion leads to quantifiable improvements in left ventricular function.[29] However, the return of atrial contraction may be delayed or insufficient if AF has been present for a substantial period of time.

Thromboembolism

The risk of stroke in non-rheumatic AF patients is 5.6 times greater than in age matched controls with an identical blood pressure distribution.[25] Thrombus formation, often in the left atrial appendage (LAA), is responsible for embolic stroke and systemic embolism in the context of AF. Stroke risk consistently and significantly increases with age from 6.7% in those aged 50–59 years to 36.2% for those aged 80–89 years.[30] Asymptomatic cerebral infarction based on computed tomography (CT) findings has been found in 14.7–48% of AF patients.[31-33] The large variation in incidence is probably due to the use of different radiological definitions of infarction and study size. The two largest studies[31,32] showed statistically significant associations of silent infarction with increasing age. Compared with non-AF strokes, those occurring in the context of AF have a greater mortality and survivors are more likely to suffer a recurrence and greater disability.[34] Asymptomatic AF carries the same thromboembolic risk as symptomatic AF. PAF has been shown also to have similar rates of ischaemic stroke and predictors as sustained AF.[35,36]

Multivariate analysis from antithrombotic trials in AF have demonstrated several clinical risk factors for stroke in non-rheumatic AF: increasing age, history of hypertension, previous stroke or transient ischaemic attack (TIA) and diabetes.[37] A pooled analysis of echocardiographic data from three of these trials demonstrated that left ventricular systolic dysfunction (as defined by global or regional wall motion abnormalities shown on 2D transthoracic echo) is an independent risk factor for stroke in AF.[38] Recent 2010 ESC guidance additionally suggests vascular disease and sex category (female) as additional important risk factors (CHA_2-DS_2-VASc scoring system; see below). Moreover, increased left atrial diameter (measured by m-mode echocardiography) is an independent predictor of thromboembolism.[39] The presence of thrombus in the LAA and its precursor, the appearance of spontaneous echo contrast, are also associated with thromboembolism.[40] Therefore, patients with AF can be risk stratified for stroke on the basis of clinical and echocardiographic data.

Clinical manifestations

AF can have a diverse clinical presentation, whether symptomatic or asymptomatic. Patients may report experiencing palpitations, dyspnoea or chest pain. Release of atrial natriuretic peptide (ANP) can be associated with polyuria, although this is relatively uncommon in the elderly. Patients may only present with the consequences of disease: thromboembolic complications, heart failure secondary to the tachycardia-induced cardiomyopathy or symptoms secondary to reduced cardiac output (lightheadedness, fatigue). Cognitive impairment secondary to cerebral hypoperfusion or recurrent thromboembolism is important to distinguish as this would identify a potentially treatable cause of impairment. Syncope is not a common presentation of AF and generally indicates additional pathology such as conduction system disease or aortic stenosis.

History and examination

There needs to be a focused workup concentrating on the following points.

Confirmation of arrhythmia

The clinician should elucidate any prior history of palpitations and associated symptoms. A review of medication past and present, for warfarin or anti-arrhythmics, should be undertaken and response/tolerance to these agents noted. On examination, there is an irregularly irregular pulse and variation in loudness of the first heart sound. There is good evidence that manual pulse check with ECG follow-up of an irregular pulse is a sensitive screening method.[41] A 12-lead ECG is essential, as this

can provide evidence of prior myocardial infarction, left ventricular hypertrophy and AV node or bundle branch conduction disease.

Aetiology of arrhythmia

It is essential to identify any possible reversible triggers that may be responsible for a new episode of AF or deterioration in previously well-controlled disease. An assessment of associated cardiovascular disease should also be made both for aetiology and stroke risk assessment.

Effect of arrhythmia on the patient

It is important to identify a clear pattern of symptoms attributable to the arrhythmia and any indication of cardiovascular compromise. Evidence of end-organ effects such as heart failure or stroke should also be sought, as this may influence treatment decisions such as anticoagulation.

Patient assessment for management options

A balanced decision regarding rate versus rhythm control and the risks and benefits of anticoagulation should be made. It is imperative that any potential bleeding risks (such as previous haemorrhage or history of falls) are identified. A social history (emphasizing exercise tolerance, living conditions, access to support and cognitive function) is important. A review of medication will establish potential risks of drug interactions and polypharmacy. Issues of non-compliance should be explored as medication, particularly warfarin, will require stable and consistent administration.

Imaging

Transthoracic echocardiography (TTE) is an essential investigation in any patient with AF, regardless of age. It provides an assessment of the left atrium, mitral valve and left ventricular function and dimensions, thus providing information regarding aetiology and stroke risk assessment. TTE has its limitations since it cannot reliably exclude the presence of thrombus in the LAA. Transoesophageal echocardiography (TOE) is the imaging of choice to examine the LAA for thrombus or its precursor spontaneous echo contrast. Its role in cardioversion is discussed below.

Other tests

A chest X ray and lung function tests are required when lung disease is suspected. A CT head scan is indicated if there is any evidence of cerebrovascular disease which may be important in making a decision regarding anticoagulation. Relevant blood and urine tests include those to rule out infection or inflammatory disorders, liver and renal functions, thyroid functions, full blood count and coagulation profile.

Management

There are two aims in the management of AF: to prevent thromboembolism and to control the arrhythmia (rate or rhythm control). The classification of AF into paroxysmal, persistent, long-standing persistent and permanent is clinically useful as it gives a clear guide to a management strategy for each patient. In PAF, the aim is to maintain sinus rhythm and control the ventricular rate when AF does occur. For a patient with permanent AF, the decision has been made to accept the arrhythmia and instead symptomatic improvement is attained with ventricular rate control. Persistent AF may presents the clinician with a dilemma: standard practice has been to strive for sinus rhythm by electrical or pharmacological means with symptom control, improved haemodynamics and reduced risk of thromboembolism being the proposed rationale. However, rhythm control medication could pose the problem of pro-arrhythmia and randomized controlled trials[42–47] have not shown superiority of rhythm control over rate control; these are summarized in Table 36.3.

The conclusion to draw from these trials is that for relatively asymptomatic elderly patients with persistent AF, rate control is generally no worse an option than rhythm control. In a first detected episode of AF, one should consider an attempt at rhythm control, cardioversion being the first-line therapy for acute haemodynamic compromise related to AF. However, in elderly patients who are tolerating the arrhythmia, accepting rate control should not be viewed as a failure. Acceptable methods of rate and rhythm control for the elderly are described in the following section. Anticoagulation to prevent thromboembolism needs to be considered whichever strategy is chosen. How a patient is anticoagulated will depend upon the options available, duration of anticoagulation and a risk–benefit analysis for each patient.

Rate control

As has already been discussed, bradycardia is not a normal finding for the elderly and similarly a slow ventricular rate in an elderly patient with untreated AF implies underlying conduction system disease.[48] The aim of rate control is to maintain a patient's heart rate at what is physiologically appropriate for the level of exertion. This must not be at the expense of symptomatic pauses or bradycardia. Therapy must be tailored to the individual, but rates of 60–80 bpm at rest and 90–115 bpm during moderate exercise have been suggested as a target.[49] This can be achieved through medication and/or non-pharmacological methods, although not infrequently no specific rate control therapy is needed in the elderly. The recent RACE II trial[50] showed that in patients with fast ventricular rates, but without severe symptoms,

Table 36.3 Randomized controlled trials of rate versus rhythm control in AF.

Trial[a]	No. of patients	Mean age (years)	Follow-up (years)	Outcome
AFFIRM AF + risk factor for stroke	4060	69.7	3.5	No difference on overall mortality or quality of life Increased hospitalization in rhythm control group
PIAF Persistent AF + symptoms	252	61	1	No difference in symptoms or quality of life Increased hospitalization in rhythm control group Increased walking distance in rhythm control group
RACE Persistent AF or flutter post-cardioversion	522	68	2.3	No difference in composite end-points (cardiovascular death, heart failure, thromboembolism, bleeding, severe drug adverse effects, pacemaker implantation)
STAF Persistent AF + symptoms + LVEF <45%	200	65	1.6	No difference in composite end-points (death, cerebrovascular event, systemic embolization, cardiopulmonary resuscitation) Increased hospitalization in rhythm control group
HOT-CAFÉ First clinically overt persistent AF	205	60.8	1.7	No difference in composite end-points of death, thromboembolic events, intracranial or major haemorrhage
AF–CHF AF + symptoms of heart failure + LVEF ≤ 35%	1376	66	3.1	No difference in cardiovascular deaths

[a]AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management;[43] PIAF, Pharmacological Intervention in Atrial Fibrillation;[42] RACE, Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation;[44] STAF, Strategies of Treatment of Atrial Fibrillation;[45] HOT-CAFÉ, How to Treat Chronic Atrial Fibrillation;[46] AF-CHF, Atrial Fibrillation–Congestive Heart Failure;[47] LVEF, left ventricular ejection fraction.

stringent rate control (resting heart rate <80 bpm) conferred no symptomatic benefit over lenient rate control (resting heart rate <110 bpm).

Digoxin

Digoxin, a muscarinic agonist, slows AV nodal conduction. This is sufficient to produce adequate rate control for elderly patients with low levels of exertion. This action can be overwhelmed when faced with high sympathetic stimulation, which explains why digoxin is less effective during exercise and why patients with previously well-controlled AF present with inadequate rate control in the context of an acute illness.[51] Although digoxin can be considered as first-line therapy for an inactive elderly patient, it should not be solely relied upon in the presence of high sympathetic tone (i.e. sepsis, pain, β-agonist medication). Digoxin also blocks the sodium/potassium ATPase exchange pump by occupying the potassium binding site (hence digoxin toxicity is potentiated in hypokalaemia) and can act as a mild positive ionotrope (although probably not in the context of AF). Digoxin has not been shown to be of prognostic benefit in heart failure[52] but it can be safely used in patients with heart failure. In comparison with β-blockers and the non-DHP calcium channel antagonists used for rate control, digoxin has a relatively slow onset of action of the order of hours compared with minutes.[48] This is acceptable if there is no urgency for rate control to be achieved. Digoxin compared with placebo produces a small but statistically significant reduction in the frequency of symptomatic episodes of PAF,[53] probably via a significant reduction in ventricular rate, recorded during patient-activated recordings. However, 24 h ambulatory ECG monitoring during this period failed to show any reduction in frequency, duration of AF or ventricular rate. Digoxin was well tolerated by these patients and so is not believed to be detrimental in PAF, although its benefit is questionable. Concerns have been expressed regarding its use in PAF, as digoxin has been shown to augment the shortening in atrial effective refractory period that can predispose to further episodes of AF.[54] Digoxin has no role to play in cardioversion. Neither oral[55] nor intravenous[56] preparations have been shown to be more effective than placebo. Digoxin is excreted in an unchanged form via the kidneys. Serum level monitoring and dose adjustment will be required in renal dysfunction. To reduce the risk of toxicity, a lower dosage than that required in younger patients should initially be used. The dose may then be up-titrated if the response is inadequate. There is an age-related decline in glomerular filtration rate and impaired renal function can easily develop with acute illness or changes to medication, such as introduction of a diuretic.

β-Blockers

β-Receptor antagonists block the action of catecholamines and hence are particularly useful in the context of high sympathetic drive. This may on occasion also be to their detriment as a decrease in maximum exercise tolerance has been reported,[57] as have measured reductions in $VO_{2\,max}$ and cardiac output during exercise.[58] A reduction in exercise tolerance is not universal, however, and β-blockers remain the most effective agent for controlling ventricular rate during exertion. They should also be considered as first-line treatment in the context of hypertension, ischaemic heart disease or stable LV dysfunction, although usually more β-blockade is needed for rate control than for heart failure and so β-blocker monotherapy is not useful for patients with both conditions. These agents have a rapid onset of action, but their use is restricted by bronchospasm. In cases of acute pulmonary oedema, they should only be considered where there is no doubt that it is has been precipitated by decompensated AF (not an easy diagnosis to be certain of) and used in small, titrated doses.

Non-dihydropyridine calcium channel antagonists

Verapamil and diltiazem act directly on the AV node, slowing conduction. Both have a rapid onset of action similar to that of β-blockers and are a useful alternative in the context of airways disease. These too should be used with caution in pulmonary oedema and do not have the prognostic benefits enjoyed by β-blockers in heart disease.

Amiodarone

In cases where amiodarone fails to cardiovert AF chemically, significant improvements in ventricular rate control can occur.[59] This is clinically useful where rapid control of AF is required to relieve symptoms and effective rate control can provide a significant benefit, even if cardioversion is unsuccessful. However, for the purposes of rate control, the agents discussed above are a more practical long-term option as the use of amiodarone maybe limited due to severe extracardiac side effects, including thyroid dysfunction.

Dronedarone

This is a new multichannel blocker that is used for maintaining sinus rhythm, but also has anti-adrenergic activity and is effective as a rate-controlling agent during rest as well as exercise. It can be added to other rate-controlling agents and effectively reduces heart rates in AF relapses (not currently approved for permanent AF).[60]

Combination of rate control agents

A combination of β-blocker and non-DHP calcium channel antagonists is to be used only with caution. These are both negative ionotropes, which together can cause life-threatening hypotension or bradycardia. In addition, verapamil and diltiazem both inhibit the metabolism of propranolol and metoprolol and hence if used together can result in synergistic detrimental effects.[61] Verapamil can cause a significant and unpredictable elevation in plasma digoxin levels and should not be used together. There are, however, no significant interactions of digoxin with diltiazem,[62] making it a preferred option over verapamil. Digoxin can also be used in combination with β-blockers, but vigilant follow-up is required for any of these combinations as the risk of conduction disease and hence the potential for bradyarrhythmias are more common in elderly patients. Amiodarone causes significant elevation in the plasma levels of digoxin, necessitating halving of the digoxin dose if used simultaneously with amiodarone.[61]

Recommendations for rate control

Monotherapy for ventricular rate control should be chosen on an individual basis: digoxin is recommended for relatively sedentary patients with low levels of exertion, β-blockers for active patients or those with ischaemic heart disease, and calcium channel antagonists (diltiazem or verapamil) if β-blockers are not tolerated or are contraindicated.

Combination therapy of the above may be required to achieve adequate rate control at rest and during exercise, with careful monitoring to avoid bradycardia. Amiodarone is also an effective rate-controlling agent and may be suitable for some patients when other drugs are unsuccessful. In certain situations, such as heart failure, combination of a β-blocker with digoxin may be beneficial.

For acute rate control in patients without heart failure or hypotension, intravenous β-blocker or calcium channel antagonist (diltiazem or verapamil) can be used. In patients where adequate rate control cannot be achieved or medication is not tolerated, non-pharmacological methods should be considered.

Non-pharmacological rate control

Permanent pacemaker

In the elderly, AF may be a part of wider conduction system disease ('tachy-brady syndrome', sick sinus syndrome) and adequate rate control may only be achieved at the expense of intolerant bradycardia. Implantation of a permanent pacemaker may then become necessary to allow continuation or up-titration of rate-control medication.

Ablate and pace strategy

If the ventricular response is refractory to medical rate control therapy or a patient is intolerant to drug therapy and other non-pharmacological treatments such as catheter-based or surgical ablation of AF are not indicated, the option of catheter-based ablation of AV node/bundle of His should be considered. The main benefits of this

approach are a reduction in symptoms and improved quality of life.[63] This involves irreversible destruction of normal AV conduction tissue, an irreversible process that renders the patient permanently pacemaker dependent. Cardiac resynchronization therapy (biventricular pacemaker) may provide additional long-term benefit in patients with severe heart failure symptoms (NYHA functional class III or IV) and LV ejection fraction ≤35%.

Rhythm control

Urgent DC cardioversion (DCC)

Patients with acute, uncontrolled AF who become haemodynamically compromised or experience evolving myocardial ischaemia/infarction require urgent synchronized electrical DCC under short-acting general anaesthetic or conscious sedation. Unless AF duration is <48 h or if the patient is not already anticoagulated within the therapeutic range, then the procedure should be preceded by an intravenous bolus of unfractionated heparin followed by either continuous infusion or subcutaneous low molecular weight heparin (LMWH). A prospective study of 357 patients (mean age 68 years) presenting with AF of duration that was clinically estimated at <48 h and without prior anticoagulation demonstrated a low incidence of thromboembolism with cardioversion.[64] If the duration of arrhythmia is uncertain or when there is high risk of left atrial/atrial appendage thrombus, transoesophageal echocardiography can be performed prior to urgent cardioversion. Electrical cardioversion can cause temporary disruption of left atrial mechanical function, which can lead to the development of spontaneous echo contrast and thrombus formation. Therefore, despite the low incidence of thrombus formation in AF of <48 h duration, thromboembolic risk becomes evident in the period after cardioversion. The duration of risk is uncertain, especially in cases of cardioversion for acute AF. A retrospective, pooled analysis of studies of electrical cardioversion of AF of various durations demonstrated that 98% of embolic episodes occurred within 10 days of cardioversion.[65] Current recommendations are to commence oral anticoagulation with warfarin and maintain an international normalized ratio (INR) of 2–3 for at least 4 weeks after cardioversion, except when AF is of recent onset and no other thromboembolic risk factors are present.[18]

Elective DC cardioversion

Elective cardioversion should be considered for patients with AF who are stable and do not have severe underlying heart disease. At least 3 weeks of adequate anticoagulation with warfarin is mandatory prior to attempted cardioversion of AF of >48 h duration. This been shown successfully to resolve preformed atrial thrombus and results in an 87% improvement in the incidence of thromboembolism at cardioversion.[66] Some trials have shown that an alternative strategy of transoesophageal echo-guided cardioversion to exclude the presence of LAA thrombus obviates the need for prior anticoagulation, is safe, reduces the time to cardioversion, is associated with fewer haemorrhagic events[67] and is cost-effective.[68] Timing of recovery of left atrial mechanical function is related to duration of prior AF.[29] If the patient remains in sinus rhythm at 4 weeks post-cardioversion, anticoagulation may be stopped depending on long-term thromboembolic risk. However, as discussed above, the duration of thromboembolic risk still remains uncertain. In the Rate Control versus Electrical Cardioversion trial,[44] 17% of all thromboembolic complications occurred in the rhythm control arm when warfarin therapy was ceased. Electrolyte imbalances must be excluded prior to an attempt at cardioversion. Cardioversion generally achieves high success rates,[69] but relapse rates can be high with age, hypertension, AF duration, previous recurrences, enlarged left atrium, presence of coronary disease, pulmonary or mitral valve disease and NYHA functional class III or IV predicting long-term failure of electrical cardioversion.[70] In the event of relapse, further attempts at cardioversion with pretreatment with anti-arrhythmic medication are recommended.[49] Amiodarone would be a suitable choice for the elderly patient, but consideration must be paid to the risks of such a strategy (pro-arrhythmia/systemic side effects) as compared with accepting rate control for each individual patient.

Pharmacological cardioversion and rhythm control

The risk of thromboembolism is present irrespective of the method of cardioversion employed, requiring anticoagulation use with pharmacological attempts at rhythm control. The choice of agents that can be used in elderly patients is more restricted than that for younger patients with AF. This is because of the increased comorbidity in the elderly population and the side-effect profile of medication used.

Amiodarone

This Vaughan Williams class III anti-arrhythmic, along with sotalol and dofetilide, blocks potassium channels, thereby slowing repolarization and prolonging the QT interval. It also affects calcium and sodium channels and has an extensive half-life (~50 days) due to protein binding. It has a broad side-effect profile but a practical safety profile, permitting its use in LV dysfunction and ischaemic heart disease. It is indicated for both cardioversion and maintenance of sinus rhythm. Amiodarone is metabolized by the cytochrome P450 system and so the dosage may have to be increased when used concomitantly with enzyme inducers such as rifampicin or carbamazepine. Amiodarone itself is an enzyme inhibitor, resulting in increased drug levels of phenytoin or warfarin if used in combination. It is important to consider that because of its long half-life, side

Table 36.4 Factors which increase the risk of sotalol-induced QT prolongation and pro-arrhythmia.

- Women
- Marked left ventricular hypertrophy (>1.4 cm)
- Severe bradycardia
- Ventricular arrhythmias
- Renal dysfunction
- Hypokalaemia
- Hypomagnesaemia

effects or interactions may persist for some time, even after discontinuation of the amiodarone. Risk of drug-induced pro-arrhythmia (QT prolongation and polymorphic ventricular tachycardia), although less in comparison with other anti-arrhythmic drugs, requires regular monitoring of QT interval.

Sotalol

Another potassium channel blocker, sotalol has additional β-blocking action (class II) that predominates over the class III action at low doses. This may limit its efficacy in the elderly population where intolerance of substantial β-blocker action may prevent high enough dosing for the class III effect to manifest. Sotalol appears to be as effective as amiodarone in patients with ischaemic heart disease (SAFE-T study[71]) and should be used as first-line agent in these patients.

Sotalol prolongs the QT interval, which should be closely monitored and the drug stopped or reduced if the QT interval is >500 ms (Table 36.4).

β-Blockers

β-Blockers are only modestly effective in preventing recurrent AF, except if it is related to thyrotoxicosis or is exercise induced. The 'anti-arrhythmic' effect may also be due in part to better rate control during paroxysmal episodes rendering these recurrences less symptomatic or silent.

Flecainide

The class 1C anti-arrhythmic flecainide is a sodium channel blocker that delays depolarization and can lead to prolongation of the QRS width. In suitable patients with AF <24 h, intravenous flecainide has 67–92% efficacy in converting AF to sinus rhythm, but is less effective in AF of longer duration. In the light of the Cardiac Arrhythmia Suppression Trial (CAST), where flecainide in post-infarct patients was associated with increased mortality,[72] concern has been expressed regarding its safety for use in the elderly, who will generally have a degree of ischaemic heart disease. Flecainide should be avoided in patients with coronary artery disease or left ventricular impairment. The drug prolongs the QRS duration, and thereby the QT interval, and should be stopped if the QRS duration has increased by >25% of the baseline.

Dofetilide/ibutilide

These are a newer class III agents that may be effective in recent-onset AF. Ibutilide is more effective in conversion of atrial flutter than AF. However, a high incidence of ventricular arrhythmias currently limits their use in elderly patients.

Dronedarone

Dronedarone is a new multichannel blocker that is less toxic than amiodarone, in terms of systemic side effects, and may be of use to maintain sinus rhythm in stable patients without structural heart disease or heart failure. In comparison with placebo, dronedarone appears to reduce significantly all-cause mortality, cardiovascular hospitalizations and stroke risk (independent of antithrombotic treatment) in patients with paroxysmal or persistent AF or flutter (ATHENA study[73]).

Similarly to sotalol and flecainide, dronedarone is less effective than amiodarone in maintaining sinus rhythm.[74] However, it may be more important from a general perspective, especially in the elderly, to have less cardiovascular hospitalizations or stroke risk than maintenance of sinus rhythm when other relevant therapies for rate control and anticoagulation are well maintained. Dronedarone can be safely prescribed in patients with NYHA class I–II heart failure, but there is increased mortality when used in symptomatic patients with NYHA class III–IV heart failure due to worsening of heart failure (ANDROMEDA study[75]). Although studies included patients with a history of risk factors such as hypertension and coronary disease, no definitive data exist for its use in patients with LVH or in those who are asymptomatic to justify routine prescribing.

Recommendations for rhythm control

Urgent electrical cardioversion should be considered for AF resulting in haemodynamic compromise, myocardial ischaemia or heart failure. Elective electrical or pharmacological cardioversion should be considered for patients with stable AF where there is a reasonable chance of long-term maintenance of sinus rhythm. Premedication with anti-arrhythmic medication increases the success rate in maintaining sinus rhythm after electrical cardioversion. The choice of pharmacological agent for long-term control is limited in the elderly due to underlying heart disease. β-Blockers should be considered for rhythm (plus rate) control in patients with a first episode of AF. Amiodarone is suitable for patients with left ventricular dysfunction, whereas sotalol is preferred in patients with ischaemic heart disease in the absence of significant left ventricular hypertrophy or impairment. Dronedarone use is limited to patients without significant structural heart disease, but

should be considered in order to reduce cardiovascular admissions in patients with paroxysmal/persistent AF and cardiovascular risk factors.

Non-pharmacological rhythm control

A number of non-pharmacological options have been explored to control and prevent AF, with varying degrees of success. Currently these procedures are not widely suitable for an elderly population, but can be considered on an individual basis.

Ablation procedures (surgical and catheter based)

For its continuation, AF needs a critical mass of atrial tissue to allow the spread of multiple waves of depolarization.[76] The maze operation has been developed and refined whereby multiple atrial incisions are made to interrupt abnormal conduction pathways, but maintain a route for sinus impulses from the SA node to pass to the AV node. The procedure achieves maintenance of sinus rhythm at 3 months in >90% of selected patients[77] and freedom from AF for up to 15 years in 75–95%. The major drawback is the requirement for median sternotomy and the use of cardiopulmonary bypass. This has limited its use to patients who are already requiring cardiac surgery for another indication such as valve replacement. Catheter-based approaches have attempted to duplicate the maze procedure without requiring extensive surgery and procedures targeting the left atrium have had more success than those in the right atrium.[49] The potential application of catheter ablation has grown since the detection of ectopic beats originating from pulmonary veins that are capable of instigating AF. Short-term studies have shown success in the mapping and ablation of foci for PAF.[78,79] Refinements need to be made to the localization of foci and choice of energy source used (radiofrequency, laser or cryoablation). The procedure is time consuming; there is a substantial risk of pulmonary vein stenosis, thromboembolism and damage to adjacent structures,[80] but it may prove useful in selected patients with non-permanent AF. With improvements in technology and our understanding of mechanisms of AF, catheter ablation is assuming an increasing role in AF management. Recent meta-analysis found a 77% success rate for catheter ablation versus 52% for anti-arrhythmic therapy.[81]

Nevertheless, the success rates are generally higher in younger patients with relatively normal hearts. Unlike younger patients, factors that initiate and maintain AF in the elderly are not just limited to triggers found within the pulmonary veins, but also within the atrial substrate requiring more extensive ablation and repeat procedures. Currently, most of the elderly population may not benefit from catheter-based techniques. Atrial flutter commonly coexists with AF, but can be more symptomatic than AF. Catheter ablation of atrial flutter, on the other hand, is relatively safer and quicker with high success rates even in the elderly population.

Atrial pacing

It has been reported that atrial (including dual-chamber) pacing has reduced the incidence of AF versus ventricular pacing alone in patients receiving a permanent pacemaker for sick sinus syndrome. Large trials have had conflicting results with reports of reduced incidence of AF[13,15,82] and no reported differences (UKPACE[16]). No trial has yet shown a statistically significant reduction in mortality. Therefore, in those patients receiving a pacemaker for sinus node dysfunction, atrial pacing could be considered to reduce the incidence of AF. This does not translate to AF patients who do not require a pacemaker for another clinical indication. The importance of the site of atrial pacing and multisite atrial pacing is being investigated and may find a future role in patients with symptomatic, drug-refractory AF.[83]

Anticoagulation

A large body of evidence exists for the use of antithrombotic therapy in AF to prevent thromboembolic stroke. Current options for thromboprophylaxis are vitamin K antagonists (VKA) such as adjusted-dose warfarin (INR 2–3) or antiplatelet agents such as aspirin (75–325 mg daily). A recent meta-analysis demonstrated that adjusted-dose warfarin reduced the relative risk of stroke by 64%.[84] Antiplatelet therapy, aspirin being the most commonly studied agent, reduces stroke risk by 22%. Aspirin 75 mg achieves near-complete platelet inhibition and is safer than higher doses in terms of bleeding risk. The benefits are consistent for both primary and secondary prevention.

Adjusted-dose warfarin or aspirin?

A meta-analysis of nine clinical trials comparing VKA and aspirin revealed significant superiority of VKA over aspirin with a relative risk reduction (RRR) of 39%. In the Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA[85]), VKA (INR 2–3) was superior to aspirin 75 mg daily by 52% in reducing primary endpoints of ischaemic or haemorrhagic strokes or systemic embolism. There was no difference between VKA or aspirin in risk of major haemorrhage.

In the ACTIVE trials, anticoagulation was superior to combined aspirin–clopidogrel (ACTIVE-W, RRR 40%) with no difference in bleeding rates.[86] In the ACTIVE-A study (aspirin–clopidogrel versus aspirin alone), combination therapy reduced the stroke risk by 28% at the expense of a 2% increase in major bleeding events.[87a]

Table 36.5 CHA_2DS_2-VASc risk factor-based scoring system.

Risk factor	Score[a]
*C*ongestive cardiac failure	1
*H*ypertension	1
*A*ge >75 years	2
*D*iabetes mellitus	1
*S*troke/TIA/thromboembolism	2
*V*ascular disease (myocardial infarction/peripheral arterial disease/aortic plaques)	1
*A*ge 65–74 years	1
*S*ex category (i.e. female sex)	1

[a]Maximum score 9 as age may score 0, 1 or 2.

VKA treatment should be considered for all patients with AF or flutter, including elderly patients, with ≥1 stroke risk factors in the absence of contraindications after assessment of risk–benefits and patient preferences. It is important to note that the type of AF does not influence the decision for thromboprophylaxis. The choice between VKA and aspirin (or other antiplatelet drugs) depends on the number of risk factors for thromboembolic events present in a given patient. The $CHADS_2$ scoring system is widely used and serves as a simple tool to guide antithrombotic treatment (1 point each for *C*ardiac failure, *H*ypertension, *A*ge >75 years and *D*iabetes and 2 points for history of *S*troke). A score of ≥2 requires use of VKA, with aspirin or VKA for score 1 and aspirin or no antithrombotic therapy for score 0. Age >75 years independently carries a worse prognosis for stroke and mortality over other risk factors. The $CHADS_2$ system can underestimate the stroke risk, placing some patients in the 0–1 category who may significantly benefit from anticoagulation. Recent AF guidelines have addressed this issue and advise a more comprehensive risk-factor-based approach using a modified scoring system (CHA_2DS_2-VASc; see Table 36.5) in patients who score 0–1 on the $CHADS_2$ system (ESC guidelines for AF[18]).

Underuse of warfarin in the elderly

There is considerable evidence for the under use of warfarin, especially in the elderly, due to presumed risk of bleeding. In a survey of the prevalence of AF and eligibility for anticoagulation in Newcastle, UK, only 17% of patients aged over 75 years with AF and no irreversible contraindications were receiving warfarin.[88] A prospective study of 1138 stroke patients admitted to a neurology unit observed that only 12% of patients with AF who suffered a recurrent stroke were receiving warfarin prior to their recurrence.[89] An American physicians' survey reported that not only was older age a deterrent to providing anticoagulation, but also a lower intensity of anticoagulation was sought.[90]

Anticoagulation issues in the elderly

Risk of bleeding and warfarin dose

Bleeding risk has inconsistently been associated with increasing age. Recent studies show considerably lower rates of intracranial haemorrhage between 0.1 and 0.6% in the elderly population on anticoagulation maintained on INR 2.0–3.0.[91] While taking warfarin, most episodes of thrombosis occur at INR levels of <2,[92] but intracranial bleeding increases significantly with INR values >3.5–4.0. The SPAF III study[93,94] investigated the efficacy of low-intensity fixed-dose warfarin (INR 1.2–1.5) plus aspirin 325 mg versus adjusted-dose warfarin. The low-dose regimen was associated with a significantly higher incidence of stroke or thromboembolism. The Primary prevention of Arterial Thromboembolism in patients with non-valvular Atrial Fibrillation (PATAF) study[95] showed no difference between aspirin 150 mg, adjusted-dose warfarin and low-dose warfarin, but excluded patients aged over 78 years from the study, so the results cannot be applied to the elderly.

The key hurdle, however, is trying to maintain a patient's INR within the range 2–3. In the SPAF III study, only 61% of INR measurements were in that range.

Practicalities of regular monitoring in the elderly

Standard monitoring of INR has taken place in the haematology-based anticoagulation clinic. Like most hospital outpatient clinics, these can be extremely busy, have inflexibility in appointment times and dates and can represent a significant challenge for the elderly patient. Where difficulties are perceived, this may even influence the decision to anticoagulate a patient with warfarin. This need not be the case and availability and ease of use can be improved by disseminating the responsibility for monitoring into the community. Reliable and portable machines for measuring prothrombin times are available[96] and dose adjustments can be made by general practitioners or non-clinicians such as pharmacists[97] at practices or visiting nursing homes.

Pharmacokinetics of warfarin in the elderly

Cross-sectional and longitudinal[98] studies have both reported a fall in warfarin dose requirements with increasing age. Conclusive mechanisms are yet to be fully elucidated, but reduced drug clearance will play a role in the elderly. Although this does not influence the achievement of a steady state of anticoagulation, it does affect how the anticoagulation is induced. The commonly used Fennerty regimen[99] was first described in patients with a mean age of 52 years. A low-dose induction regimen has been shown to induce fewer INR measurements >4.5 and spend more time within the therapeutic range for

patients aged over 75 years.[100] This was achieved at the expense of an increase in mean time to reach therapeutic INR, which although on average was less than a single day,[100] may present an unacceptable delay in discharge from hospital.

Pharmacodynamics of warfarin the elderly

Issues of non-compliance or inconsistencies in consumption of tablets in elderly patients with dementia are a particular concern for warfarin, a drug with considerable individual variation and a narrow therapeutic window where a greater or lesser effect both carry significant risk. In a study of long-term care facilities, those patients with AF who were also diagnosed as having dementia were less likely to receive warfarin.[101] Clearly, dementia can encompass a wide range of degrees of cognitive impairment and no one would argue that in the presence of end-stage dementia the benefits of anticoagulation for AF would outweigh the discomfort and inconvenience of regular monitoring and minor bleeding. However, in the context of multi-infarct dementia, the benefits of anticoagulation to halt the stepwise decline become more apparent. Indeed, a supervised residential facility provides an environment where compliance issues can be managed.

Risks associated with polypharmacy

Numerous interactions have been reported with warfarin. Table 36.6 lists common agents involved, but is not intended as a comprehensive list. The anticoagulant effect will be reduced by foods that are high in vitamin K such as parsley, broccoli and liver. Polypharmacy and the risk of falls have to be considered with sedative medication or postural hypotension secondary to antihypertensives.

Upcoming anticoagulants

Several new oral anticoagulants are being developed which are at least as effective as VKA, with less drug interaction and better pharmacokinetics negating the need for regular INR monitoring. These include direct thrombin inhibitors (e.g. dabigatran) and factor Xa inhibitors (e.g. rivaroxaban, apixaban). In the RE-LY study, dabigatran 110 mg b.i.d. was similar to VKA in stroke prevention with lower bleeding rates. Higher dose of 150 mg b.i.d. further lowered the risk of thromboembolic stroke with similar major bleeding rates to those with VKA.[87b] AVERROES study compared apixaban against aspirin in patients unsuitable for VKA and showed significant reductions in stroke and systemic embolism with an acceptable safety profile.[102]

Non-pharmacological possibilities to prevent stroke

As LAA is the major site for development of atrial thrombus, mechanical occlusion of LAA may reduce the risk of stroke in patients with AF. Catheter-based occlusion of the LAA (WATCHMAN device) in high-risk patients who are unsuitable for VKA showed non-inferiority to VKA, but at higher rates of adverse events, mainly due to procedure-related complications.[103] More evidence is needed to allow the routine use of such devices.

Other supraventricular arrhythmias

As discussed above, the most common supraventricular arrhythmia in the elderly is atrial fibrillation. Paroxysmal atrioventricular nodal reciprocating tachycardia (AVNRT) is more common in the younger age groups than in the elderly. AVNRT may commonly manifest at later ages in association with coronary disease, perioperatively or chest infection. AVNRT is recognized on the ECG as rapid, narrow, complex tachycardia. Small, inverted P waves are generally seen superimposed on the terminal portion of the QRS complex. The diagnostic challenge is when a supraventricular tachycardia presents as a broad complex tachycardia due to aberrant conduction from partially blocked right or the left bundle branches, when it will need to be distinguished from a ventricular tachycardia (VT). Both arrhythmias can be asymptomatic or symptomatic and it is safer to assume all broad complex tachycardias to be ventricular in origin until proven otherwise. In general, dissociate atrial and ventricular activity (including fusion or capture beats), concordant QRS pattern in precordial leads, prominent R wave in V1, QRS morphology similar to previously noted ventricular ectopy, electrolyte disturbances and presence of acute myocardial ischaemia favour the diagnosis of VT.

Patients with SVT and haemodynamic instability require urgent DCC. In stable patients, vagal manoeuvres such as

Table 36.6 Common medication which interact with warfarin.

System	Potentiate anticoagulation	Decrease anticoagulation
Cardiovascular	Amiodarone, simvastatin, fibrates	Spironolactone
Endocrine	Thyroxine, steroids	
Gastrointestinal	Cimetidine, omeprazole	Cholestyramine
Nervous	Chlorpromazine, tricyclic antidepressants	Barbiturates, carbamazepine
Malignancy	Tamoxifen	
Antimicrobials	Aminoglycosides, metronidazole, clarithromycin	Rifampicin

carotid massage or the valsalva manoeuvre could terminate the tachycardia, failing which intravenous β-blockers, non-dihydropyridine calcium channel blockers (verapamil, diltiazem) or adenosine may be necessary. In patients without any history of severe asthma or obstructive airway disease, adenosine is preferred due to its short half-life and rapid onset of action. For long-term management and prevention of future recurrences, the choice generally lies between β-blockers, verapamil and diltiazem. Amiodarone or sotalol may be considered in selected patients, but increase the risk of systemic side effects or pro-arrhythmia.

Ventricular arrhythmias

Ventricular arrhythmias are common in the elderly and the incidence increases with advancing age and the presence of structural heart disease.[104] A ventricular ectopic beat or premature ventricular contraction (PVC) is a depolarization that originates in the ventricles, has a wide QRS complex and is followed by a normal compensatory pause (see Figure 36.8). Three or more consecutively occurring PVCs with a rate in excess of 120 bpm is termed *ventricular tachycardia* (VT). VT is defined as non-sustained (NSVT) if lasting <30 s (see Figure 36.9) and sustained if lasting >30 s or requiring immediate cardioversion. VT is characterized by an ECG appearance of a broad, complex tachycardia with QRS duration >0.12 s (an important differential to consider is supraventricular tachycardia with aberrant conduction). VT is monomorphic if the QRS morphology remains stable or polymorphic if QRS morphology is variable (e.g. torsades de pointes – polymorphic VT with changing QRS axis). Complex ventricular arrhythmias include VT and paired, multiform or frequent PVCs. Ventricular fibrillation is rapid (>300 bpm), irregular complexes with marked variation in rate, amplitude and morphology (Figure 36.10).

Ventricular arrhythmias can be found in 70–80% of people over 60 years of age. Complex ventricular ectopy is common in the elderly, but many often remain asymptomatic. Incidence of sudden cardiac death (SCD) increases with age and 80% of SCDs from cardiac causes can be attributed to coronary heart disease, other common causes being dilated or hypertrophic cardiomyopathy and valvular heart disease. In the peri-infarction period, age >75 years appears to be independently associated with higher in-hospital cardiac arrest.[105] Channelopathies, such as congenital long QT or Brugada syndromes, are uncommon in the elderly age group.

Prognosis

PVDs and non-sustained VT in the absence of heart disease are not associated with an increase in coronary disease or mortality and do not require treatment with anti-arrhythmic medication.[106] In contrast, polymorphic VT

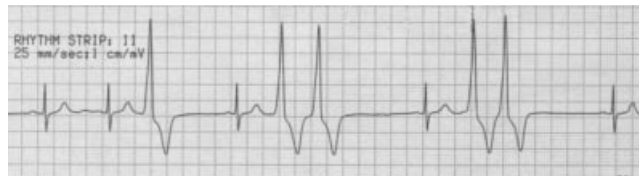

Figure 36.8 Rhythm strip showing single and paired ventricular ectopic beats followed by normal compensatory pauses.

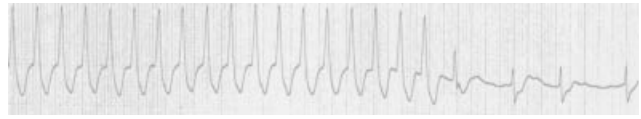

Figure 36.9 Rhythm strip showing non-sustained ventricular tachycardia.

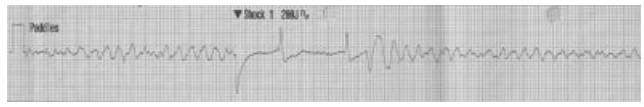

Figure 36.10 Ventricular fibrillation.

even in the absence of heart disease is an indicator of risk. It is important to note that frequent PVCs or VT may occur as a consequence of electrolyte imbalance or drug adverse effect. In patients who have a history of previous myocardial infarction, the frequency of PVDs (>10 per hour), runs of PVDs or NSVT and reduced left ventricular ejection fraction are all independently associated with new coronary events and mortality.[107,108] Ventricular arrhythmias during first 24–48 h after acute myocardial infarction do not indicate continuing risk. In patients with non-ST elevation myocardial infarction, the long-term risk and mortality are variable and may depend on the extent of initial myocardial damage.

Pathogenesis

For a ventricular tachyarrhythmia to develop, a substrate and a triggering factor are required. The substrate can either be structural (infarcted or hypertrophic myocardium resulting in myocytes of differing refractory periods forming a potential re-entrant circuit) or electrical (the occurrence of early or delayed after-depolarizations). The triggering factor is typically a transient influence such as electrolyte imbalance, acute ischemia or even an anti-arrhythmic medication, such as in the case of torsades de pointes.

Management

Appropriate management of ventricular arrhythmias requires not only knowledge of aetiology and mechanism

of the arrhythmia, but also an understanding of other associated medical problems and the risk–benefit profile of any anti-arrhythmic therapy. The presence of reversible precipitants needs to be excluded. Treatment of heart failure, myocardial ischaemia, drug toxicity, electrolyte imbalance (e.g. hypo- or hyperkalaemia, hypomagnesaemia) can abolish or reduce the occurrences of ventricular arrhythmias. Investigations include serum electrolyte levels, 12-lead or ambulatory ECG monitoring, exercise testing to exclude cardiac ischaemia or to diagnose exercise-related arrhythmias, cardiac catheterization, echocardiography or other forms of imaging (MRI, perfusion scans) and electrophysiological testing.

The ultimate aim should be to prevent such an arrhythmia occurring in the first instance. Overall management of ventricular arrhythmias in the elderly does not differ from that recommended for the general population, but necessitates taking into account other factors such as involvement of other organ systems, presence of other comorbidities and physiological changes that occur with advancing age. These factors strongly influence the choice and appropriateness of any pharmacological or non-pharmacological management.

Drug therapy

With the exception of β-blockers, currently available anti-arrhythmic drugs have not shown any prognostic benefit in the management of complex ventricular arrhythmias or prevention of SCD. As a general rule, anti-arrhythmic drugs are recommended as adjunctive therapy to β-blockers due to potential pro-arrhythmic or systemic side effects. There is increased susceptibility to adverse cardiac events with advancing age, particularly in relation to class Ic anti-arrhythmic drugs (e.g. flecainide; Vaughan Williams classification). Sotalol is less frequently used in the elderly due to a propensity towards pro-arrhythmia by increasing the QT interval, especially in the presence electrolyte imbalance or other major organ involvement. Treatment with flecainide[109] or D-sotalol,[110] despite successfully suppressing PVDs, both agents lead to an increased mortality in patients after myocardial infarction as compared with placebo. In survivors of cardiac arrest, amiodarone may improve prognosis.[11] A meta-analysis of 13 randomized controlled trials of prophylactic amiodarone in patients with recent myocardial infarction or congestive heart failure demonstrated a statistically significant relative risk reduction of 29% in arrhythmic/sudden death.[112] A relative risk reduction in total mortality of 13–15% was marginal, but importantly there was no increase in non-arrhythmic deaths. However, two large primary prevention trials of amiodarone post-myocardial infarction both demonstrated reductions in arrhythmic deaths, but had no effect on total mortality,[113,114] raising concerns that reductions in fatal arrhythmias are offset by increased mortality from other causes. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT),[115] a, primary prevention study comparing placebo, amiodarone and implantable cardioverter defibrillator (ICD) in patients with NYHA functional class II or III and left ventricular ejection fraction (EF) <35%, amiodarone failed to show reduction in all-cause mortality compared with placebo.

Therefore, amiodarone, with which there is considerable clinical experience in the treatment of ventricular tachycardia, is useful in preventing arrhythmic deaths and is safe in the context of ischaemia and heart failure, but the beneficial effect on total mortality appears to be small with too little evidence to justify its routine prophylactic use.[116]

Amiodarone is associated with many side effects, particularly in elderly patients who are already on multiple drug therapy, increasing the risk of drug interaction. Systemic side effects of amiodarone include thyroid and liver dysfunction, skin sensitivity and corneal deposits.

β-Blockers remain the mainstay of treating ventricular arrhythmias and, either alone or in combination with non-arrhythmic agents (ACE inhibitors, angiotensin receptor blockers, statins), have consistently been shown to reduce SCD and all-cause mortality in patients with heart failure or after myocardial infarction in all age groups, including the elderly. There is also some evidence that omega-3 polyunsaturated fatty acids and statins may have anti-arrhythmic properties of their own due to a membrane-stabilizing effect.

Despite the proven efficacy of β-blockers, these agents remain underused in the elderly population with an independent negative association with age. A retrospective analysis on use of β-blockers after myocardial infarction in patients >65 years of age found that only 21% of 3737 patients received β-blockers despite the absence of any contraindications. The study also found 43% lower 2 year mortality in those who had received β-blockers.[117]

Role of implantable cardioverter defibrillator

Beyond medication, the ICD has now emerged as the most effective therapy for primary and secondary prevention of fatal ventricular tachyarrhythmias (see Figures 36.11 and 36.12). The addition of an antitachycardia pacing facility can effectively terminate some tachyarrhythmias prior to shock delivery. The primary prevention Multicenter Automatic Defibrillator Implantation Trial (MADIT)[118] and Multicenter Unsustained Tachycardia Trial (MUSTT)[119] studies have both demonstrated statistically significant reductions in overall mortality as compared to anti-arrhythmic medication in patients with previous myocardial infarction (MI), reduced LV ejection fraction and non-sustained VT who were referred for electrophysiological studies (EPS). The subsequent MADIT 2 study[120] enrolled patients with prior

Figure 36.11 Implantable cardioverter defibrillator.

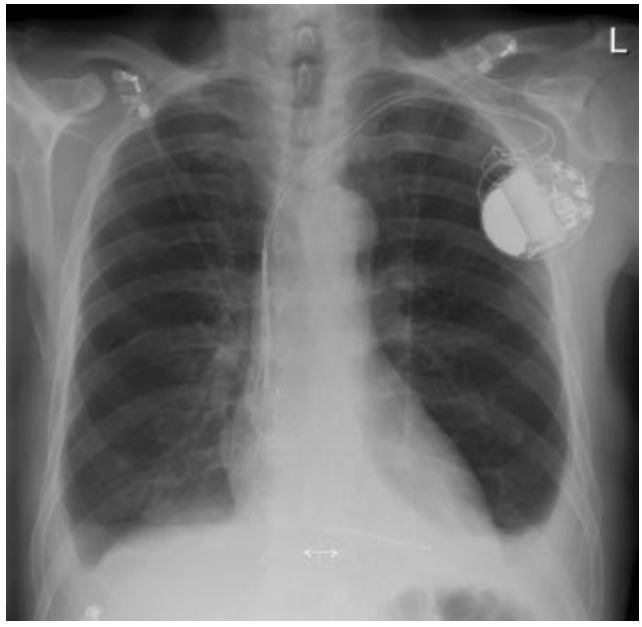

Figure 36.12 Chest X-ray of a patient with an ICD (atrial and ventricular leads).

MI and ejection fraction <30% with no requirement for the occurrence of ventricular arrhythmia or need for EPS. There was a statistically significant reduction in overall mortality as compared to conventional medical therapy alone, which persisted for both sexes in all age groups in subgroup analysis.

Two major trials have now defined the role of ICD therapy for primary prevention in patients with dilated cardiomyopathy (DCM). The SCD-HeFT consisted of 2521 patients with a mean age of 60 years. It included patients with ischaemic DCM, no history of prior sustained VT or VF, left ventricular ejection fraction <35% and NYHA functional class II or III on optimal medical therapy with ACE inhibitor and β-blocker use. ICD therapy was associated with a statistically significant reduction in all-cause mortality compared with best medical therapy alone or in combination with amiodarone.[115] The Defibrillators in Non-ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) consisted of patients with non-ischaemic DCM on optimal heart failure medication including ACE inhibitor and β-blocker, but not on amiodarone therapy. ICD therapy was associated with a statistically significant reduction in arrhythmic death compared with best medical therapy alone, but only a trend towards reduction in all-cause mortality. Based on these data, ICD therapy should be considered on an individual basis for patients with severe left ventricular dysfunction and non-ischaemic DCM.[121]

There have been three prospective randomized trials comparing ICD therapy with medication for secondary prevention. The Anti-arrhythmics Versus Implantable Defibrillators (AVID) trial[122] was the largest of these and was the only one to show a statistically significant risk reduction in mortality with ICD therapy compared with medication. Patients with episodes of VF or haemodynamically significant VT were randomized to ICD or anti-arrhythmic medication (amiodarone or sotalol). The majority of patients had ischaemic heart disease and the mean left ventricular ejection fraction (LVEF) was 32%. The mean age of participants was 65 years, but subgroup analysis showed no difference in outcome for those aged over 70 years. The Canadian Implantable Defibrillator Study (CIDS) trial[123] included patients with syncope probably secondary to VT and compared ICD therapy with amiodarone. In a multivariate analysis of CIDS,[124] the patients at highest risk of cardiovascular death (age ≥70 years, LVEF ≤35% and NYHA class III or IV) were found to benefit the most from ICD therapy. The Cardiac Arrest Study Hamburg (CASH) trial[125] also had metoprolol and propafenone treatment limbs. The propafenone limb was stopped early because of excess mortality. A meta-analysis of these trials concluded a 28% relative reduction in death with ICD therapy in patients with LVEF of <35%.[126]

Implantable cardioverter defibrillators in the elderly

All major ICD trials have included a substantial number of patients >65 years of age. Subgroup analyses of these trials show equivalent benefit from ICD between younger and elderly populations and it is appropriate to consider ICD implantation irrespective of the age. Nevertheless, ICD remains an invasive treatment that may not be suitable for all. There are sparse data on the procedure-related morbidity in the elderly. As previously discussed in the section on AF, the very elderly can present additional challenges

that have to be taken into account when analysing the risk versus benefits for any given therapy. Regular follow-up at a tertiary centre clinic is vital to ensure that the device continues to function effectively and safely. Appropriate and inappropriate shocks may prove intolerable for some patients and an ICD would be unsuitable for those with significant dementia or other major comorbidities with a projected lifespan of <1 year. Any reduction in medication will be beneficial in the elderly, but anti-arrhythmics may still be required in some patients to reduce the burden of arrhythmia and hence the shock frequency. Further studies will have to be undertaken to help further risk stratify elderly patients and identify those most likely to benefit from an ICD, but age alone is not a contraindication for this therapy. There are widening indications for implantation of ICD and selected elderly patients can gain significantly from the treatment.

Key points

- Arrhythmias are common in the elderly.
- The heart is subject to both ageing and disease-related changes that predispose to arrhythmia generation and persistence.
- Atrial fibrillation is the most common sustained arrhythmia in the elderly and carries a substantial risk of morbidity and mortality from thromboembolic stroke.
- Presence or absence of non-cardiac comorbidities in the elderly play a major role, not only in the genesis of arrhythmias, but also in their specific management based on assessment of risks versus benefits for each individual patient.

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CHAPTER 37

Ischaemic heart disease

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Introduction

The most common cause of death in elderly persons is ischaemic heart disease (IHD). Coronary atherosclerosis is very common in the elderly, with autopsy studies demonstrating a prevalence of at least 70% in persons older than 70 years. The prevalence of IHD is similar in elderly women and men.[1] In one study, clinical IHD was present in 502 of 1160 men (43%), mean age 80 years, and in 1019 of 2464 women (41%), mean age 81 years. At 46-month follow-up, the incidence of new coronary events (myocardial infarction or sudden cardiac death) was 46% in the elderly men and 44% in the elderly women.[1]

IHD is diagnosed in elderly persons if they have either coronary angiographic evidence of significant IHD, a documented myocardial infarction (MI), a typical history of angina pectoris with myocardial ischaemia diagnosed by stress testing, or sudden cardiac death. The incidence of sudden cardiac death as the first clinical manifestation of IHD increases with age.

Clinical manifestations

Dyspnoea on exertion is a more common clinical manifestation of IHD in elderly persons than is the typical chest pain of angina pectoris. The dyspnoea is usually exertional and is related to a transient rise in left ventricular (LV) end-diastolic pressure caused by ischaemia superimposed on decreased LV compliance. Because elderly persons are more limited in their activities, angina pectoris in elderly persons is less often associated with exertion. Elderly persons with angina pectoris are less likely to have substernal chest pain, and they describe their anginal pain as less severe and of shorter duration than do younger persons. Angina pectoris in elderly persons may occur as a burning post-prandial epigastric pain or as pain in the back or shoulders. Acute pulmonary oedema unassociated with an acute MI may be a clinical manifestation of unstable angina pectoris due to extensive IHD in elderly persons.

Myocardial ischaemia, appearing as shoulder or back pain in elderly persons, may be misdiagnosed as degenerative joint disease. Myocardial ischaemia, appearing as epigastric pain, may be misdiagnosed as peptic ulcer disease. Nocturnal or post-prandial epigastric discomfort that is burning in quality may be misdiagnosed as hiatus hernia or oesophageal reflux instead of myocardial ischaemia due to IHD. The presence of comorbid conditions in elderly persons may also lead to misdiagnosis of symptoms due to myocardial ischaemia.

Elderly persons with IHD may have silent or asymptomatic myocardial ischaemia. In a prospective study, 133 of 195 men (34%), mean age 80 years, with IHD and 256 of 771 women (33%), mean age 81 years, with IHD had silent myocardial ischaemia detected by 24-hour ambulatory electrocardiograms (ECGs). At 45-month follow-up, the incidence of new coronary events in elderly men with IHD was 90% in men with silent myocardial ischaemia versus 44% in men without silent ischaemia. At 47-month follow-up, the incidence of new coronary events in elderly women with IHD was 88% in women with silent ischaemia versus 43% in women without silent ischaemia.[2]

Recognized and unrecognized MI

Pathy demonstrated in 387 elderly patients with acute MI that 19% had chest pain, 56% had dyspnoea or neurological symptoms or gastrointestinal symptoms, 8% had sudden death, and 17% had other symptoms.[3] Another study showed in 110 elderly patients with acute MI that 21% had no symptoms, 22% had chest pain, 35% had dyspnoea, 18% had neurological symptoms, and 4% had gastrointestinal symptoms (Table 37.1).[3] Other studies have also shown a high prevalence of dyspnoea and neurological symptoms in elderly patients with acute MI.[3] In these studies, dyspnoea was present in 22% of 87 patients, in 42% of 777 patients, and in 57% of 96 patients. Neurological

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 37.1 Presenting symptoms in 110 elderly patients with acute myocardial infarction.

Dyspnoea was present in 35% of patients
Chest pain was present in 22% of patients
Neurological symptoms were present in 18% of patients
Gastrointestinal symptoms were present in 4% of patients
No symptoms were present in 21% of patients

Source: Paper by Aronow WS discussed in Aronow and Fleg, 2008.[3]

symptoms were present in 16% of 87 patients, in 30% of 777 patients, and in 34% of 96 patients.

As with myocardial ischaemia, some patients with acute MI may be completely asymptomatic or the symptoms may be so vague that they are unrecognized by the patient or physician as an acute MI. Studies have reported that 21–68% of MIs in elderly patients are unrecognized or silent.[3] These studies also demonstrated that the incidence of new coronary events including recurrent myocardial infarction, ventricular fibrillation and sudden death in patients with unrecognized MI, is similar to that in patients with recognized MI.

Diagnostic techniques

Resting ECG

In addition to diagnosing recent or prior MI, the resting ECG may show ischaemic ST-segment depression, arrhythmias, conduction defects, and LV hypertrophy that are related to subsequent coronary events. At 37-month mean follow-up, elderly patients with ischaemic ST-segment depression 1 mm or greater on the resting ECG were 3.1 times more likely to develop new coronary events than were elderly patients with no significant ST-segment depression.[3] Elderly patients with ischaemic ST-segment depression 0.5 to 0.9 mm on the resting ECG were 1.9 times more likely to develop new coronary events during 37-month follow-up than were elderly patients with no significant ST-segment depression. At 45-month mean follow-up, pacemaker rhythm, atrial fibrillation, premature ventricular complexes, left bundle branch block, intraventricular conduction defect, and type II second-degree atrioventricular block were associated with a higher incidence of new coronary events in patients.[3] Numerous studies have also documented that elderly patients with ECG LV hypertrophy have an increased incidence of new coronary events.[3]

Many studies have shown that complex ventricular arrhythmias in elderly persons with IHD are associated with an increased incidence of new coronary events including sudden cardiac death.[3] The incidence of new coronary events is especially increased in elderly persons with complex ventricular arrhythmias and abnormal LV ejection fraction or LV hypertrophy. At 45-month follow-up of 395 men, mean age 80 years, with IHD, complex ventricular arrhythmias detected by 24-hour ambulatory ECGs increased the incidence of new coronary events 2.4 times.[4] At 47-month follow-up of 771 women, mean age 81 years, with IHD, complex ventricular arrhythmias detected by 24-hour ambulatory ECGs increased the incidence of new coronary events 2.5 times.[4]

Exercise stress testing

Hlatky *et al*. found the exercise ECG to have a sensitivity of 84% and a specificity of 70% for the diagnosis of IHD in persons older than 60 years of age.[3] Newman and Phillips found a sensitivity of 85%, a specificity of 56%, and a positive predictive value of 86% for the exercise ECG in diagnosing IHD.[3] The increased sensitivity of the exercise ECG with increasing age found in these two treadmill exercise studies was probably due to the increased prevalence and severity of IHD in elderly persons.

Exercise stress testing also has prognostic value in elderly patients with IHD. Deckers *et al*.[3] showed that the one-year mortality was 4% for 48 patients 65 years of age or older who were able to do an exercise stress test after acute MI and 37% for the 63 elderly patients unable to do the exercise stress test after acute MI.

Exercise stress testing using thallium perfusion scintigraphy, radionuclide ventriculography, and echocardiography are also useful in the diagnosis and prognosis of CHD. Iskandirian *et al*.[3] showed that exercise thallium-201 imaging can be used for risk stratification of elderly patients with IHD. The risk for cardiac death or non-fatal MI at 25-month follow-up in 449 patients 60 years of age or older was less than 1% in patients with normal images, 5% in patients with single-vessel thallium-201 abnormality, and 13% in patients with multivessel thallium-201 abnormality.

Pharmacological stress testing

Intravenous dipyridamole-thallium imaging may be used to determine the presence of IHD in elderly patients who are unable to undergo treadmill or bicycle exercise stress testing. In patients 70 years of age or older, the sensitivity of intravenous dipyridamole-thallium imaging for diagnosing significant IHD was 86%, and the specificity was 75%.[3] In 120 patients older than 70 years, adenosine echocardiography had a 66% sensitivity and a 90% specificity in diagnosing IHD.[3] An abnormal adenosine echocardiogram predicted a threefold risk of future coronary events, independent of coronary risk factors.[3] In 120 patients older than 70 years, dobutamine echocardiography had a 87% sensitivity and a 84% specificity in diagnosing IHD.[3] An

abnormal dobutamine echocardiogram predicted a 7.3-fold risk of future coronary events.[3]

Signal-averaged electrocardiography

Signal-averaged electrocardiography (SAECG) was performed in 121 elderly post-infarction patients with asymptomatic complex ventricular arrhythmias detected by 24-hour ambulatory ECGs and a LV ejection fraction of 40% or higher.[3] At 29-month follow-up, the sensitivity, specificity, positive predictive value, and negative predictive value for predicting sudden cardiac death were 52%, 68%, 32%, and 83%, respectively for a positive SAECG; 63%, 70%, 38%, and 87%, respectively for non-sustained ventricular tachycardia; and 26%, 89%, 41%, and 81%, respectively for a positive SAECG plus non-sustained ventricular tachycardia.[3]

Coronary risk factors

Cigarette smoking

The Cardiovascular Health Study demonstrated in 5201 men and women 65 years of age or older that >50 pack-years of smoking increased five-year mortality 1.6 times.[5] The Systolic Hypertension in the Elderly Program pilot project showed that smoking was a predictor of first cardiovascular event and MI/sudden death.[5] At five-year follow-up of 7178 persons ≥65 years of age in three communities, the relative risk for CVD mortality was 2.0 for male smokers and 1.6 for female smokers.[5] The incidence of CVD mortality in former smokers was similar to those who had never smoked.[5] At 40-month follow-up of 664 men, mean age 80 years, and at 48-month follow-up of 1488 women, mean age 82 years, current cigarette smoking increased the relative risk of new coronary events 2.2 times in men and 2.0 times in women.[6] At six-year follow-up of older men and women in the Coronary Artery Surgery Study registry, the relative risk of MI or death was 1.5 for persons 65–69 years of age and 2.9 for persons 70 years of age and older who continued smoking compared with quitters during the year before study enrolment.[5]

Elderly men and women who smoke cigarettes should be strongly encouraged to stop smoking to reduce the development of IHD. Smoking cessation will decrease mortality from IHD, other cardiovascular disease, and all-cause mortality in elderly men and women. A smoking cessation programme should strongly be recommended.

Hypertension

Systolic hypertension in elderly persons is diagnosed if the systolic blood pressure is 140 mmHg or higher from two or more readings on two or more visits.[7] Diastolic hypertension in elderly persons is similarly diagnosed if the diastolic blood pressure is 90 mmHg or higher. In a study of 1819 persons, mean age 80 years, living in the community, the prevalence of hypertension was 71% in elderly African Americans, 64% in elderly Asians, 62% in elderly Hispanics, and 52% in elderly whites.[5] Isolated systolic hypertension in elderly persons is diagnosed if the systolic blood pressure is 140 mmHg or higher with a diastolic blood pressure of less than 90 mmHg. Approximately two-thirds of elderly persons with hypertension have isolated systolic hypertension.

Isolated systolic hypertension and diastolic hypertension are both associated with increased IHD morbidity and mortality in elderly persons.[5] Increased systolic blood pressure is a greater risk factor for IHD morbidity and mortality than is increased diastolic blood pressure. The higher the systolic or diastolic blood pressure, the greater the morbidity and mortality from IHD in elderly women and men. The Cardiovascular Health Study demonstrated in 5202 elderly men and women that a brachial systolic blood pressure >169 mmHg was associated with a 2.4-fold greater five-year mortality.[5]

At 30-year follow-up of persons 65 years of age and older in the Framingham Heart Study, systolic hypertension was related to a greater incidence of IHD in elderly men and women.[5] Diastolic hypertension correlated with the incidence of IHD in elderly men but not in elderly women. At 40-month follow-up of 664 elderly men and 48-month follow-up of 1488 elderly women, systolic or diastolic hypertension was associated with a relative risk of new coronary events of 2.0 in men and 1.6 in women.[6] Data from Framingham also suggests the importance of increased pulse pressure, a measure of large artery stiffness. Among 1924 men and women aged 50–79 years, at any given level of systolic blood pressure of 120 mmHg or greater, the risk of IHD over 20 years rose with lower diastolic blood pressure, suggesting that higher pulse pressure was an important component of risk.[5] Among 1061 men and women aged 60–79 years in the Framingham Heart Study, the strongest predictor of IHD risk was pulse pressure [hazard ratio(HR) = 1.24].

Elderly persons with hypertension should be treated with salt restriction, weight reduction if necessary, discontinuation of drugs that increase blood pressure, avoidance of alcohol and tobacco, increase in physical activity, decrease of dietary saturated fat and cholesterol, and maintenance of adequate dietary potassium, calcium and magnesium intake. In addition, antihypertensive drugs have been shown to reduce IHD events in elderly men and in elderly women with hypertension.[7,8]

Despite multiple large randomized trials, treatment of hypertension in patients aged 80 years or older remained controversial until the publication of HYVET.[8] In HYVET, 3845 persons aged 80 years and older (mean age 83.6 years)

with a sustained systolic blood pressure of 160 mmHg or higher were randomized to indapamide (sustained-release 1.5 mg) or matching placebo. Perindopril 2 mg or 4 mg, or matching placebo, was added if needed to achieve the target blood pressure of 150/80 mmHg. The study was terminated early after a median follow-up of 1.8 years.

Antihypertensive drug treatment reduced the incidence of the primary endpoint (fatal or non-fatal stroke) by 30%, fatal stroke by 39%, all-cause mortality by 21%, death from cardiovascular causes by 23%, and heart failure by 64%. The significant 21% reduction in all-cause mortality by antihypertensive drug treatment was unexpected. The benefits of antihypertensive drug treatment appeared during the first year of follow-up.

The prevalence of cardiovascular disease was only 12% at baseline in HYVET patients (i.e. much lower than generally reported in community-based samples of octogenarians). For example, in a cohort of patients with hypertension, mean age 80 years, in a university geriatrics practice, 70% had cardiovascular disease, target organ damage, or diabetes mellitus.[5] The absolute reduction in cardiovascular events resulting from antihypertensive drug therapy in an elderly population with a high prevalence of cardiovascular disease could be much greater than observed in HYVET.

Elderly persons with IHD should have their blood pressure reduced to <135/85 mmHg and to less than 130/80 mmHg if diabetes mellitus or chronic renal disease is present.[7] JNC 7 pointed out that most patients with hypertension will require two or more antihypertensive drugs to achieve this blood pressure goal.[7] The drugs of choice for treating IHD with hypertension are beta-blockers and angiotensin-converting enzyme (ACE) inhibitors. If a third antihypertensive drug is needed, a thiazide diuretic should be administered.

Left ventricular hypertrophy

Elderly men and women with ECG LV hypertrophy and echocardiographic LV hypertrophy have an increased risk of developing new coronary events.[5] At four-year follow-up of 406 elderly men and 735 elderly women in the Framingham study, echocardiographic LV hypertrophy was 15.3 times more sensitive in predicting new coronary events in elderly men and 4.3 times more sensitive in predicting new coronary events in elderly women than was electrocardiographic LV hypertrophy.[5] At 37-month follow-up of 360 men and women, mean age 82 years, with hypertension or IHD, echocardiographic LV hypertrophy was 4.3 times more sensitive in predicting new coronary events than was electrocardiographic LV hypertrophy.[5]

Physicians should try to prevent LV hypertrophy from developing or progressing in elderly men and women with IHD. A meta-analysis of 109 treatment studies found that ACE inhibitors were more effective than other antihypertensive drugs in decreasing LV mass.[5]

Dyslipidemia

Numerous studies have demonstrated that a high serum total cholesterol is a risk factor for new or recurrent coronary events in elderly men and women.[5] At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1488 elderly women, an increment of 10 mg dl^{-1} of serum total cholesterol was associated with an increase in the relative risk of 1.12 for new coronary events in both men and in women.[6]

A low serum high-density lipoprotein (HDL) cholesterol is a risk factor for new coronary events in elderly men and women.[5] In the Framingham study, in the Established Populations for Epidemiologic Studies of the Elderly study, and in a large cohort of convalescent home patients,[5] a low serum HDL cholesterol was a more powerful predictor of new coronary events than was serum total cholesterol. At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1488 elderly women, a decrement of 10 mg dl^{-1} of serum HDL cholesterol increased the relative risk of new coronary events 1.70 times in men and 1.95 times in women.[6]

Hypertriglyceridemia is a risk factor for new coronary events in elderly women but not in elderly men.[5] At 40-month follow-up of elderly men and at 48-month follow-up of elderly women, the level of serum triglycerides was not a risk factor for new coronary events in men and was a very weak risk factor for new coronary events in women.[6]

Numerous studies have demonstrated that statins reduce new coronary events in elderly men and in elderly women with IHD.[9] The absolute reduction in new coronary events in these studies is greater for elderly persons than for younger persons. In an observational prospective study of 488 men and 922 women, mean age 81 years, with prior MI and a serum low-density lipoprotein (LDL) cholesterol of 125 mg dl^{-1} or higher, 48% of persons were treated with statins.[10] At three-year follow-up, statins reduced new coronary events by 50%. The lower the LDL cholesterol achieved by statin therapy, the greater the reduction in coronary events in elderly patients with prior MI.[10]

Current guidelines recommend lipid-lowering therapy in elderly men and women with IHD to reduce their serum LDL cholesterol to less than 70 mg dl^{-1}.[11,12] Data from the Heart Protection Study suggest that elderly men and women with IHD should be treated with statins regardless of initial levels of serum lipids.[13]

Diabetes mellitus

Diabetes mellitus is a risk factor for new coronary events in elderly men and women.[5] In the Cardiovascular Health

Study, an elevated fasting glucose level (>130 mg dl^{-1}) increased five-year mortality 1.9 times.[5] At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1488 elderly women, diabetes mellitus increased the relative risk of new coronary events 1.9 times in men and 1.8 times in women.[6] Elderly diabetics without IHD have a higher incidence of new coronary events than elderly non-diabetics with IHD.[5]

Persons with diabetes mellitus are more often obese and have higher serum LDL cholesterol and triglyceride levels and lower serum HDL cholesterol levels than do non-diabetics. Diabetics also have a higher prevalence of hypertension and LV hypertrophy than do non-diabetics. These risk factors contribute to the increased incidence of new IHD events in diabetics compared to non-diabetics. Increased age can further amplify these risk factor differences and contribute to greater IHD risk.

Elderly persons with diabetes mellitus should be treated with dietary therapy, weight reduction if necessary, and appropriate drugs if necessary to control hyperglycaemia. The HbA1c level should be maintained at less than 7%.[5,12] Other risk factors such as smoking, hypertension, dyslipidemia, obesity and physical inactivity should be controlled. The serum LDL cholesterol level should be reduced to less than 70 mg dl^{-1}.[9,11,12] The blood pressure should be reduced to less than 130/80 mmHg. Sulfonylureas should be avoided in persons with IHD.[5]

Obesity

Obesity was an independent risk factor for new IHD events in elderly men and women in the Framingham Heart Study.[5] Disproportionate distribution of fat to the abdomen assessed by the waist:hip circumference ratio has also been shown to be a risk factor for cardiovascular disease, mortality from CHD, and total mortality in elderly men and women.[5]

Obese men and women with IHD must undergo weight reduction. Weight reduction is also a first approach to controlling mild hypertension, hyperglycaemia and dyslipidemia. Regular aerobic exercise should be used in addition to diet to treat obesity.

Physical inactivity

Physical inactivity is associated with obesity, hypertension, hyperglycaemia and dyslipidemia. At 12-year follow-up in the Honolulu Heart Program, physically active men 65 years of age or older had a relative risk of 0.43 for IHD compared with inactive men.[5] Lack of moderate or vigorous exercise increased five-year mortality in elderly men and women in the Cardiovascular Heart Study.[5]

Moderate exercise programmes suitable for elderly persons include walking, climbing stairs, swimming or bicycling. However, care must be taken in prescribing any exercise programme because of the high risk of injury in this age group. Group or supervised sessions, including aerobic classes, offered by senior healthcare plans are especially appealing. Exercise training programmes are not only beneficial in preventing CHD but have also been found to improve endurance and functional capacity in elderly persons after MI.[5]

Therapy of stable angina

Nitroglycerin is used for relief of the acute anginal attack. It is given either as a sublingual tablet or as a sublingual spray.[14] Long-acting nitrates prevent recurrent anginal attacks, improve exercise time until the onset of angina, and reduce exercise-induced ischaemic ST-segment depression. To prevent nitrate tolerance, it is recommended that a 12- to 14-hour nitrate-free interval be established when using long-acting nitrate preparations. During the nitrate-free interval, the use of another anti-anginal drug will be necessary.

Beta-blockers prevent recurrent anginal attacks and are the drug of choice to prevent new coronary events.[14] Beta-blockers also improve exercise time until the onset of angina and reduce exercise-induced ischaemic ST-segment depression. Beta-blockers should be administered along with long-acting nitrates to all patients with angina unless there are contraindications to the use of these drugs. Antiplatelet drugs such as aspirin or clopidogrel should also be administered to all patients with angina to reduce new coronary events.[14,15]

There are no class I indications for the use of calcium channel blockers in the treatment of patients with IHD.[12] However, if angina pectoris persists despite the use of beta blockers and nitrates, long-acting calcium-channel blockers such as diltiazem or verapamil should be used in elderly patients with IHD and normal LV systolic function and amlodipine or felodipine in patients with IHD and abnormal LV systolic function as anti-anginal agents.

If angina persists despite intensive medical management, coronary revascularization with either coronary angioplasty or coronary artery bypass surgery should be considered.[16,17] The use of other approaches to manage angina that persists despite anti-anginal drugs and coronary revascularization is discussed elsewhere.[14]

Acute coronary syndromes

Unstable angina pectoris is a transitory syndrome that results from disruption of a coronary atherosclerotic plaque that critically decreases coronary blood flow causing new onset angina pectoris or exacerbation of angina pectoris. Transient episodes of coronary artery occlusion or near occlusion by thrombus at the site of plaque injury may

occur and cause angina pectoris at rest. The thrombus may be labile and cause temporary obstruction to flow. Release of vasoconstriction substances by platelets and vasoconstriction due to endothelial vasodilator dysfunction contribute to a further reduction in coronary blood flow, and in some patients, myocardial necrosis with non-ST-elevation myocardial infarction (NSTEMI) occurs. Elevation of serum cardiospecific troponin I or T or creatine kinase-MB levels occur in patients with NSTEMI but not in patients with unstable angina.

Older patients with unstable angina pectoris should be hospitalized, and depending on their risk stratification, may need monitoring in an intensive care unit. In a prospective study of 177 consecutive unselected patients hospitalized for an acute coronary syndrome (91 women and 86 men) aged 70–94 years, unstable angina was diagnosed in 54%, NSTEMI in 34%, and ST-segment elevation myocardial infarction (STEMI) in 12%.[18] Obstructive IHD was diagnosed by coronary angiography in 94% of elderly men and in 80% of elderly women.

Therapy

Treatment of patients with unstable angina pectoris/NSTEMI should be initiated in the emergency department.[14] Reversible factors precipitating unstable angina pectoris should be identified and corrected. Oxygen should be administered to patients who have cyanosis, respiratory distress, congestive heart failure, or high-risk features. Oxygen therapy should be guided by arterial oxygen saturation and should not be given if the arterial oxygen saturation is more than 94%. Morphine sulfate should be administered intravenously when anginal chest pain is not immediately relieved with nitroglycerin or when acute pulmonary congestion and/or severe agitation is present.

Aspirin should be administered to all patients with unstable angina pectoris/NSTEMI unless contraindicated and continued indefinitely. The first dose of aspirin should be chewed rather than swallowed to ensure rapid absorption.

The American College of Cardiology (ACC)/American Heart Association (AHA) 2002 guidelines update state that clopidogrel should be administered for up to nine months in addition to indefinite use of aspirin in hospitalized patients with unstable angina pectoris/NSTEMI in whom an early non-interventional approach is planned or in whom a percutaneous coronary intervention (PCI) is planned and clopidogrel should be withheld for 5 to 7 days in patients in whom elective coronary artery surgery is planned.[19] On the basis of data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial and from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, aspirin 80 mg daily plus clopidogrel 75 mg daily should be administered to patients with unstable angina/NSTEMI for at least one year.[14]

Nitrates should be administered immediately in the emergency department to patients with unstable angina/NSTEMI.[14] Patients whose symptoms are not fully relieved with three 0.4 mg sublingual nitroglycerin tablets or spray taken five minutes apart and the initiation of an intravenous beta-blocker should be treated with continuous intravenous nitroglycerin. Topical or oral nitrates are alternatives for patients without ongoing refractory symptoms.

Beta-blockers should be administered intravenously in the emergency department unless there are contraindications to their use followed by oral administration and continued indefinitely.[14,19] Metoprolol may be given intravenously in 5 mg increments over 1 to 2 minutes and repeated every 5 minutes until 15 mg has been given followed by oral metoprolol 100 mg twice daily. The target resting heart rate is 50 to 60 beats per minute.

An oral ACE inhibitor should also be given unless there are contraindications to its use and continued indefinitely.[19] In patients with continuing or frequently recurring myocardial ischaemia despite nitrates and beta-blockers, verapamil or diltiazem should be added to their therapeutic regimen in the absence of LV systolic dysfunction (class IIa indication). The benefit of calcium-channel blockers in the treatment of unstable angina pectoris is limited to symptom control. Intra-aortic balloon pump counterpulsation should be used for severe myocardial ischaemia that is continuing or occurs frequently despite intensive medical therapy or for haemodynamic instability in patients before or after coronary angiography.[19]

A platelet glycoprotein IIb/IIIa inhibitor should also be administered in addition to aspirin and clopidogrel and heparin in patients in whom coronary angioplasty is planned.[14] Abciximab can be used for 12 to 24 hours in patients with unstable angina/NSTEMI in whom coronary angioplasty is planned within the next 24 hours. Eptifibatide or tirofiban should be administered in addition to aspirin and low-molecular-weight heparin or unfractionated heparin to patients with continuing myocardial ischaemia, an elevated cardiospecific troponin I or T, or with other high-risk features in whom an invasive management is not planned.

Intravenous thrombolytic therapy is not recommended for the treatment of unstable angina/NSTEMI.[19] Prompt coronary angiography should be performed without non-invasive risk stratification in patients who fail to stabilize with intensive medical treatment. Coronary revascularization should be performed in patients with high-risk features to reduce coronary events and mortality.[14,19]

On the basis of the available data, the ACC/AHA 2002 guidelines recommend the use of statins in patients with acute coronary syndromes and a serum LDL cholesterol of 100 mg dl^{-1} or higher 24 to 96 hours after hospitalization.[19] Statins should be continued indefinitely after hospital discharge. The ACC/AHA 2002 guidelines also recommend

use of a fibrate or nicotinic acid if the serum HDL cholesterol is less than 40 mg dl^{-1}, occurring as an isolated finding or in combination with other lipid abnormalities.

Patients should be discharged on aspirin plus clopidogrel, beta-blockers, and on ACE inhibitors in the absence of contraindications. Nitrates should be given for ischaemic symptoms. A long-acting non-dihydropyridine calcium-channel blocker may be given for ischaemic symptoms that occur despite treatment with nitrates plus beta-blockers. Hormonal therapy should not be administered to postmenopausal women.

Therapy of STEMI

Chest pain due to acute MI should be treated with morphine, nitroglycerin and beta-blockers.[20] If arterial saturation is lower than 94%, oxygen should be administered. Aspirin should be given on day 1 of an acute MI and continued indefinitely to reduce coronary events and mortality. The first dose of aspirin should be chewed rather than swallowed. Early intravenous beta-blockade should be used during acute MI and oral beta-blockers continued indefinitely to reduce coronary events and mortality. ACE inhibitors should be given within 24 hours of acute MI and continued indefinitely to reduce coronary events and mortality. Statins should be given to patients with acute MI.[9] Statins should be continued indefinitely after hospital discharge to reduce coronary events and mortality.[9]

The ACC/AHA guidelines state there are no class I indications for the use of calcium-channel blockers during or after acute MI.[21] However, if older persons have persistent angina after MI despite treatment with beta-blockers and nitrates and are not suitable candidates for coronary revascularization, or if they have hypertension inadequately controlled by other drugs, a non-dihydropyridine calcium-channel blocker such as verapamil or diltiazem should be added to the therapeutic regimen if the LVEF is normal. If the LVEF is abnormal, amlodipine or felodipine should be added to the therapeutic regimen.

The ACC/AHA guidelines recommend using intravenous heparin in persons with acute MI undergoing primary coronary angioplasty or surgical coronary revascularization and in persons with acute MI at high risk for systemic embolization such as persons with a large or anterior MI, atrial fibrillation, history of pulmonary or systemic embolus, or LV thrombus.[21] In persons with acute MI not receiving intravenous heparin, the ACC/AHA guidelines recommend using subcutaneous heparin 7500 U twice daily for 24 to 48 hours to decrease the incidence of deep venous thrombosis.[21]

Thrombolytic therapy is beneficial in the treatment of STEMI in patients younger than 75 years of age.[20,21] From the available data, one cannot conclude whether thrombolytic therapy is beneficial or harmful in patients older than 75 years with acute MI.[22] However, the data favour the use of primary coronary angioplasty in eligible patients younger and older than 75 years with acute MI to reduce coronary events and mortality.[23]

Therapy after MI

Elderly persons after MI should have their modifiable coronary risk factors intensively treated as discussed previously in this chapter. Aspirin or clopidogrel should be given indefinitely to reduce new coronary events and mortality.[12,15,24] The ACC/AHA guidelines recommend as class I indications for long-term oral anticoagulant therapy after MI: (1) secondary prevention of MI in post-MI patients unable to tolerate daily aspirin or clopidogrel; (2) post-MI patients with persistent atrial fibrillation; and (3) post-MI patients with LV thrombus.[21] Long-term warfarin should be given in a dose to achieve an INR between 2.0 and 3.0.

Beta-blockers (Table 37.2) and ACE inhibitors (Table 37.3) should be given indefinitely unless contraindications exist to the use of these drugs to reduce new coronary events and mortality.[12,24] Long-acting-nitrates are effective anti-anginal and anti-ischaemic drugs.[24]

There are no class I indications for the use of calcium-channel blockers after MI.[21] Teo *et al*. analyzed randomized controlled trials comprising 20 342 persons that investigated the use of calcium-channel blockers after MI.[24,25] Mortality was 4% insignificantly higher in persons treated with calcium-channel blockers. In this study, beta-blockers significantly reduced mortality by 19% in 53 268 persons. In another study, elderly persons who were treated with beta-blockers after MI had a 43% decrease in two-year mortality and a 22% decrease in two-year cardiac hospital readmissions than elderly persons who were not treated with beta-blockers.[24] Use of a calcium-channel blocker instead of a beta-blocker after MI doubled the risk of mortality.[24]

Anti-arrhythmic therapy after MI

A meta-analysis of 59 randomized controlled trials comprising 23 229 persons that investigated the use of class I anti-arrhythmic drugs after MI showed that mortality was 14% significantly higher in persons receiving class I anti-arrhythmic drugs than in persons receiving no anti-arrhythmic drugs.[25] None of the 59 studies showed a reduction in mortality by class I anti-arrhythmic drugs.

In the Cardiac Arrhythmia Suppression Trials I and II, older age also increased the likelihood of adverse effects including death in persons after MI receiving encainide, flecainide, or moricizine.[24,26] Compared with no anti-arrhythmic drug, quinidine or procainamide did not reduce mortality in elderly persons with CAD, normal or abnormal LVEF, and presence versus absence of ventricular tachycardia.[26]

Table 37.2 Effect of beta-blockers on mortality in older patients after myocardial infarction.

Study	Follow-up	Results
Goteborg Trial	90 days	Compared with placebo, metoprolol caused a 45% significant decrease in mortality in patients aged 65–74 years
Norwegian Multicentre Study	17 months (up to 33 months)	Compared with placebo, timolol caused a 43% significant reduction in mortality in patients aged 65–74 years
Norwegian Multicentre Study	61 months (up to 72 months)	Compared with placebo, timolol caused a 19% significant decrease in mortality in patients aged 65–74 years
Beta-Blocker Heart Attack Trial	25 months (up to 36 months)	Compared with placebo, propranolol caused a 33% significant reduction in mortality in patients aged 60–69 years
Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Trial	1.3 years	Compared with placebo, carvedilol caused a 23% significant reduction in mortality, a 24% significant reduction in cardiovascular mortality, a 40% significant reduction in non-fatal myocardial infarction, and a 30% significant reduction in all-cause mortality or non-fatal myocardial infarction in patients, mean age 63 years

Source: The studies are discussed in Aronow, 2008.[24]

Table 37.3 Effect of angiotensin-converting-enzyme inhibitors on mortality in older patients after myocardial infarction.

Study	Follow-up	Results
Survival and Ventricular Enlargement Trial	42 months (up to 60 months)	In patients with MI and LVEF $\leq$40%, compared with placebo, captopril reduced mortality 25% in patients aged $\geq$65 years
Acute Infarction Ramipril Efficacy Study	15 months	In patients with MI and clinical evidence of CHF, compared with placebo, ramipril decreased mortality 36% in patients aged $\geq$65 years
Survival of Myocardial Infarction Long-Term Evaluation Trial	1 year	In patients with anterior MI, compared with placebo, zofenopril reduced mortality or severe CHF 39% in patients aged $\geq$65 years
Trandolapril Cardiac Evaluation Study	24 to 50 months	In patients, mean age 68 years, with LVEF $\leq$35%, compared with placebo, trandolapril reduced mortality 33% in patients with anterior MI and 14% in patients without anterior MI
Heart Outcomes Prevention Evaluation Study	4.5 years (up to 6 years)	In patients aged $\geq$55 years with MI (53%), cardiovascular disease (88%), or diabetes (38%) but no CHF or abnormal LVEF, ramipril reduced MI, stroke, and cardiovascular death 22%
European trial on reduction of cardiac events with perindopril in patients with stable coronary artery disease	4.2 years	In patients, mean age 60 years, with coronary artery disease and no CHF, compared with placebo, perindopril reduced cardiovascular death, MI, or cardiac arrest 20%

CHF, congestive heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction
Source: The studies are discussed in Aronow, 2008.[24]

Compared with placebo, d,l-sotalol did not reduce mortality in post-MI persons followed for one year.[26] Mortality was also significantly higher at 148-day follow-up in persons treated with d-sotalol (5.0%) than in persons treated with placebo. On the basis of the available data, persons after MI should not receive class I anti-arrhythmic drugs or sotalol.

In the European Myocardial Infarction Amiodarone Trial, 1486 survivors of MI with a LV ejection fraction of 40% or less were randomized to amiodarone (743 patients) or to placebo (743 patients).[24] At two-year follow-up, 103 patients treated with amiodarone and 102 patients treated with placebo had died. In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, 1202 survivors of MI with non-sustained ventricular tachycardia or complex ventricular arrhythmias were randomized to amiodarone or to placebo.[24,26] Amiodarone was very effective in suppressing ventricular tachycardia and complex ventricular arrhythmias. However, the mortality rate at 1.8-year follow-up was not significantly different in the persons treated with amiodarone or placebo. In addition, early permanent discontinuation of drug for reasons other than outcome events occurred in 36% of persons taking amiodarone.

In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation Study, the incidence of pulmonary toxicity was 10% at two years in persons receiving

amiodarone in a mean dose of 158 mg daily.[24,26] The incidence of adverse effects for amiodarone also approaches 90% after five years of treatment. On the basis of the available data, amiodarone should not be used in the treatment of persons after MI.

However, beta-blockers have been shown to reduce mortality in persons with non-sustained ventricular tachycardia or complex ventricular arrhythmias after MI in patients with normal or abnormal LV ejection fraction.[24,26] On the basis of the available data, beta-blockers should be used in the treatment of elderly persons after MI, especially if non-sustained ventricular tachycardia or complex ventricular arrhythmias are present, unless there are specific contraindications to their use.

In the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, 1016 persons, mean age 65 years, with a history of ventricular fibrillation or serious sustained ventricular tachycardia were randomized to an automatic implantable cardioverter defibrillator (AICD) or to drug therapy with amiodarone or d,l-sotalol.[26] Persons treated with an AICD had a 39% reduction in mortality at one year, a 27% reduction in mortality at two years, and a 31% reduction in mortality at three years. If persons after MI have life-threatening ventricular tachycardia or ventricular fibrillation, an AICD should be inserted.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II randomized 1232 persons, mean age 64 years, with a prior MI and a LVEF of 30% or less to an AICD or to conventional medical therapy.[27] At 20-month follow-up, compared with conventional medical therapy, the AICD significantly decreased all-cause mortality 31% from 19.8% to 14.2%. The effect of AICD therapy in improving survival was similar in persons stratified according to age, sex, LV ejection fraction, New York Heart Association class, and QRS interval. These data favour considering the prophylactic implantation of an AICD in post-MI persons with a LVEF of 30% or lower.

Hormone replacement therapy

The Heart Estrogen/Progestin Replacement Study (HERS) investigated in 2763 women with documented IHD the effect of hormonal therapy versus double-blind placebo on coronary events.[28] At 4.1-year follow-up, there were no significant differences between hormonal therapy and placebo in the primary outcome (non-fatal MI or IHD death) or in any of the secondary cardiovascular outcomes. However, there was a 52% significantly higher incidence of non-fatal MI or death from IHD in the first year in persons treated with hormonal therapy than in persons treated with placebo. Women on hormonal therapy had a 289% significantly higher incidence of venous thromboembolic events and a 38% significantly higher incidence of gallbladder disease requiring surgery than women on placebo.

At 6.8-year follow-up in the HERS trial, hormonal therapy did not reduce the risk of cardiovascular events in women with IHD.[29] The investigators concluded that hormonal therapy should not be used to decrease the risk of coronary events in women with IHD. At 6.8-year follow-up in the HERS trial, all-cause mortality was insignificantly increased 10% by hormonal therapy. The overall incidence of venous thromboembolism at 6.8-year follow-up was significantly increased 208% by hormonal therapy. At 6.8-year follow-up, the overall incidence of biliary tract surgery was significantly increased 48%, the overall incidence for any cancer was insignificantly increased 19%, and the overall incidence for any fracture was insignificantly increased 4%.

Revascularization

Medical therapy alone is the preferred treatment in elderly persons after MI (Table 37.4). The two indications for revascularization in elderly persons after MI are prolongation of life and relief of unacceptable symptoms despite optimal medical management. In a prospective study of 305

Table 37.4 Overall medical approach to older patients after myocardial infarction.

Stop cigarette smoking and refer to smoking cessation programme.
Treat hypertension with beta-blockers and angiotensin-converting enzyme (ACE) inhibitors; the blood pressure should be reduced to $<$140/85 mmHg and to $\leq$130/80 mmHg in persons with diabetes mellitus or renal insufficiency.
The serum low-density lipoprotein cholesterol should be reduced to $<$70 mg dl^{-1} with statins if necessary and at least 30–40%.
Diabetes, obesity, and physical inactivity should be treated.
Aspirin or clopidogrel, beta-blockers, and ACE inhibitors should be given indefinitely unless contraindications exist to the use of these drugs.
Long-acting nitrates are effective anti-anginal and anti-ischaemic drugs.
There are no class I indications for the use of calcium-channel blockers after myocardial infarction (MI).
Post-infarction patients should not receive class I anti-arrhythmic drugs, sotalol, or amiodarone.
An automatic implantable cardioverter-defibrillator should be implanted in post-infarction patients at very high risk for sudden cardiac death.
Hormone replacement therapy should not be administered to postmenopausal women after MI.
The two indications for coronary revascularization in elderly persons after MI are prolongation of life and relief of unacceptable symptoms despite optimal medical management.

patients aged 75 years and older with chest pain refractory to at least two anti-anginal drugs, 150 patients were randomized to optimal medical therapy and 155 patients to invasive therapy.[30] In the invasive group, 74% had coronary revascularization (54% coronary angioplasty and 20% coronary artery bypass surgery). During the six-month follow-up, one-third of the medically treated group needed coronary revascularization for uncontrollable symptoms. At six-month follow-up, death, non-fatal MI, or hospital admission for an acute coronary syndrome was significantly higher in the medically treated group (49%) than in the invasive group (19%). Revascularization by coronary angioplasty[16] or by coronary artery bypass surgery[17] in elderly persons is extensively discussed elsewhere. If coronary revascularization is performed, aggressive medical therapy must be continued.

Key points

- Coronary risk factors should be intensively treated in elderly persons with IHD.
- Elderly persons with IHD should be treated indefinitely with antiplatelet drugs, beta-blockers, ACE inhibitors, and statins unless contraindications to the use of these drugs exist.
- The data favour the use of primary angioplasty in eligible patients younger and older than 75 years with acute MI to reduce coronary events and mortality.
- Hormone replacement therapy should not be administered to elderly women with IHD.
- The two indications for revascularization in elderly persons with IHD are prolongation of life and relief of unacceptable symptoms despite optimal medical management.

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CHAPTER 38

Lipid management

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Introduction

Atherosclerosis is a disease of ageing. Cardiovascular event rates increase in a curvilinear fashion after age 65 years in men and 75 years in women.[1–2] The decline in age-standardized cardiovascular disease (CVD)-associated death rates has shifted mortality to increasingly advanced age, with the number of cardiovascular events in those aged >80 years having increased by 60% since 1970.[3] Numerous epidemiological studies have shown that age is the principal unmodifiable risk factor for events.[4–6] Both diabetes and hypertension are strongly age-related risk factors.[7] In parallel with these risk factors levels of total cholesterol rise with age especially after middle age or the menopause. The increasing incidence of metabolic syndrome and obesity with age means that high density lipoprotein cholesterol (HDL-C) levels tend to fall and triglyceride levels rise.[8] Thus hyperlipidaemia is an increasing risk factor for coronary events, aortic valve disease, stroke, peripheral vascular disease including abdominal aortic aneurysm and possibly dementia (multi-infarct type). As many elderly patients have suffered one cardiovascular event they are at high risk of another, often in a different vascular bed. Thus patients with strokes more often have coronary events than second strokes.

As life expectancy increases, preventive efforts will become increasingly important for preventing morbidity, improving quality of life (QOL), and reducing healthcare expenditures for older persons. Clinicians need to consider additional factors in the elderly which most often are not applicable in younger individuals when faced with treatment decisions. These include co-morbid conditions, polypharmacy, drug–drug interactions and differential safety and tolerability profiles; all of which could lead to alterations in the benefit-harm balance. This highlights the importance of considering both the treatment options and the evidence for their use in the elderly population.

Cholesterol in the elderly

Ageing is associated with a progressive increase in cholesterol levels in men and in many women profound changes in lipids follow the menopause with substantial increases in low density lipoprotein cholesterol (LDL-C) secondary to possibly changes in proprotein convertase subtilisin kexin-9 (PCSK-9) levels which are under the control of sex steroids and a reduction in HDL-C most probably caused by changes in sex steroids.[9] However, most hyperlipidaemia in the elderly is still caused by dietary and lifestyle choices. The slowly declining metabolic rate of the elderly, associated with reduced levels of activity due to concurrent ageing or osteological problems means that many show features of the metabolic syndrome. Dietary conservatism also tends to mean that currently the elderly are less likely to consume a diet rich in fruit and vegetables and are more likely to eat a diet rich in saturated fat.

Secondary causes of hyperlipidaemia are more common in the elderly. The most common cause of mixed hyperlipidaemia is insulin resistance and/or type 2 diabetes. Rates of chronic renal disease also increase in the elderly, which allied to greater arterial stiffness, result in increases in pulse pressure, isolated systolic hypertension and secondary cardiovascular risk. Other causes that tend to be associated with ageing include alcohol-induced hyperlipidaemia which is more commonly due to a reduction in liver-related detoxification in the elderly and its frequent association with depression, especially in single men. Alcohol-induced hyperlipidaemia may show a profile varying between mixed hyperlipidaemia to pure hypercholesterolaemia depending on the frequency of alcohol intake. Non-alcoholic steatitic hepatitis, which is often associated with a mixed hyperlipidaemia, is more common in the centrally obese elderly.

The most common cause of pure secondary hypercholesterolaemia is hypothyroidism. The significance of this is that prescription of a lipid-lowering drug to a grossly

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hypothyroid patient massively increases their risk of drug-associated rhabdomyolysis.

However, despite these factors the positive association between total and LDL-C and cardiovascular risk attenuates with advancing age.[10] In epidemiological studies a 1 mmol l^{-1} lower total cholesterol (TC) is associated with approximately 50% reduction in coronary heart disease (CHD) mortality in patients aged 40–49 years, 33% in those aged 50–69 and 15% in those aged 70–89 years.[11] Yet, though the relative risk reduction associated with lower cholesterol decreases with age, the absolute effects of lower cholesterol on annual ischaemic heart disease mortality rates are greater in the elderly given the higher prevalence of atheroma. Also cholesterol levels decline in acute and chronic disease states, inflammation, malnutrition and cancer, all of which are more common in the elderly and thus this attenuated association may be partly due to confounding.[12]

Clinical signs

Clinical signs present differently in the elderly. Arcus senilis is associated with familial hypercholesterolaemia in the young but not in the elderly. Xanthelasma are associated with mixed dyslipidaemia and reduced skin thickness and elasticity and thus are more common in older individuals. Tendon xanthomata may be confused with gout tophi or Heberden's nodes which are common in the elderly but may be clinically distinguished by their movement with the underlying tendon.

Lipoproteins and their measurement

Blood lipids are transported in macromolecular complexes called lipoproteins. Figure 38.1 shows a schematic representation of these complex molecules. Their function is to transport triglycerides (energy) and fat soluble vitamins to sites of storage or metabolism, the principal function of the apolipoprotein B group (chylomicrons, very low density lipoprotein, low density lipoprotein (LDL)). They also function to detoxify lipopolysaccharide toxins and remove potentially toxic fatty acid metabolites – principally through reverse transport by apolipoprotein A-1 containing high density lipoproteins (HDLs). Blood lipids are most often measured either as TC, LDL, HDL as well as plasma total triglyceride (TG) components. Only the cholesterol fraction (-C) of the major lipoprotein fractions is measured routinely and the concentrations of the cholesterol subfractions do not necessarily reflect the activity of these dynamic pathways – as is most true of HDL. LDL-C is generally not measured by laboratories but calculated instead, using the Friedewald equation [LDL-C (mmol l^{-1}) = TC – (HDL-C + TG/2.20)].[13] This approximation becomes less reliable

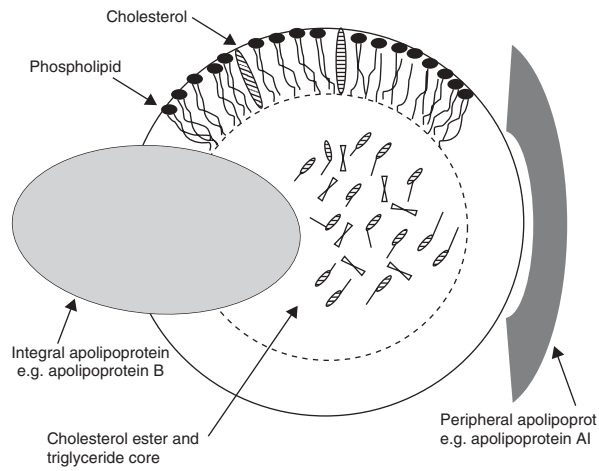

Figure 38.1 Schematic representation of a lipoprotein molecule.

at higher triglyceride concentrations (TG > 4.5 mmol l^{-1}) and cannot be used in non-fasting samples.[14]

Alternatively the concentrations of the principal proteins – apolipoproteins (apo) B and A1 can be measured and can be better measures of total CVD risk[12] analogous to the use of non-HDL cholesterol and HDL-C.[14]

Diagnosis

Lipid screening in the elderly should comprise a full profile of TC, TG and HDL-C with a calculated LDL-C. At lower levels of TC, current recommendations from the UK National Institute of Health and Clinical Excellence[15] and the Joint British Societies guidelines[16] recommend risk assessment using the Framingham (1991) equation. Treatment is recommended for any cardiovascular risk factor at 20%/future decade risk of CVD (15%/future decade risk of CHD). This approach differs from European[17] and US guidelines[18] where risk is assessed at the chronological age and treatment instituted at 20% CHD risk. It should be noted that risk assessment is an imprecise art with any estimate having a wide confidence interval.[19] The UK guidelines also adjust the risk assessment to age 70 to reduce prescribing in the otherwise fit elderly given the strong association of risk with age whereby almost any 75-year-old would require lipid-lowering. This statement is controversial and many would recommend direct assessment of plaque burdens using non-invasive techniques, for example carotid intima media thickness or coronary calcium scores.[20,21]

The risk assessment biochemical profile should include measurement of transaminases (AST/ALT), thyroid function tests and a baseline creatine kinase (CK). Lipid-lowering therapy with a statin or fibrate is contraindicated if AST/ALT exceeds 3 × upper reference limit of normal (ULN) (usually >150 IU l^{-1}). The actual contraindication is to persistent elevations in transaminases as many elevations

turn out to be transient and caused by either infections or are secondary to other drug therapies (e.g. heavy paracetamol or opiate-containing analgesic use). If gamma-glutamyl transferase is measured its level is irrelevant to starting or continuing lipid-lowering therapies.

Thyroid function tests should be measured. Gross hypothyroidism (TSH > 20 mU l^{-1}) is associated with a hypercholesterolaemia and this should be treated prior to re-measurement of the lipid profile due to the risk of lipid-lowering therapy-associated rhabdomyolysis. The risk factors for rhabdomyolysis are age, creatinine, reduced muscle mass, female sex and hypothyroidism. Mild hypothyroidism is common in the elderly and not a contraindication to lipid-lowering therapies though some reports suggest that reports of myalgia may be more common in patients with borderline hypothyroidism.

The significance of CK measurement in the elderly is debated. Lipid-lowering therapies are contraindicated in patients with CK > × 10 ULN though most clinicians are reluctant to prescribe if 5 × ULN. Some elevated CK measurements, for example in Africans or Afro-Caribbeans, represent normal variants. In other patients a mildly elevated CK allied with a mild adverse reaction to lipid-lowering therapies should prompt investigation for rheumatological causes of disease as the lipid-lowering therapy may have uncovered this predisposition.

LDL-C as a target of therapy with statins

Epidemiological studies incriminate high levels of LDL-C as being atherogenic with the serum TC as a good correlate for LDL-C levels.[18] However, the definitive proof has come from clinical trial work of lipid-lowering interventions which has been hailed as one of the major advances in clinical medicine. Whether cholesterol is lowered by diet, drugs, or other means, CVD risk decreases.[22] Comparing earlier trials of statins, and other treatment modalities such as bile acid sequestrant resins and ileal bypass surgery with more recent statin trials, the benefit of absolute LDL-C reduction is present across a wide range of baseline concentrations.

Statins

Statins form the cornerstone of pharmaceutical CVD prevention. These agents have shown to reduce the risk of both CHD and stroke in clinical trials enrolling persons aged up to age 80 years (Table 38.1). A meta-analysis of 90 056 patients which included 14 randomized trials showed that those aged >65 years (n = 6446) had 19% reduction in the risk of major cardiovascular events, a benefit similar to the 22% reduction in risk experienced by those aged <65 years (n = 7902).[23] Earlier secondary prevention statin trials, such as the Scandinavian Simvastatin Survival Study (4S),[24] Cholesterol and Recurrent Events (CARE),[25] and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID),[26] support a benefit of lipid lowering after MI. Although these trials excluded patients >75 years of age (4S upper age limit, 69 years), subgroup analysis demonstrated a benefit of statins among younger elderly.[27,28] More data on statin therapy in the elderly became available following the Heart Protection Study which randomized more than 20 000 participants with known CVD or diabetes to either simvastatin 40 mg or placebo in the age range 40–80 (85 by trial end).[29] Simvastatin reduced the risk of cardiovascular events by 18% in those aged 70 to 80 years (n = 5806) compared with 24% in those aged <65 years. The apparent attenuated impact of simvastatin in the older age group was not statistically significant. As the elderly have a higher absolute risk of events the number of events prevented in those aged >70 years and in those aged <70 years were similar. More evidence on the benefits of statin intervention in the elderly accumulated following the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), which was specifically aimed at evaluating the efficacy of statin use in the elderly.[30] In this study 5804 subjects between the ages 70–82 years with pre-existing CHD or at high risk for CHD were randomized to 40 mg of pravastatin or placebo. Over an average of more than three years follow-up, the pravastatin group had significantly fewer combined cardiovascular outcomes (CHD death or non-fatal or fatal myocardial infarction, fatal or non-fatal stroke). The question as to whether older individuals without evidence of CVD will benefit from statin treatment (i.e. in the primary prevention setting)[31] was answered by the recent Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.[32] This study compared rosuvastatin 20 mg to placebo in 17 802 apparently healthy participants with relatively low LDL-C levels of <3.4 mmol l^{-1} and high sensitivity C-reactive greater than 2 mg l^{-1}. The composite primary cardiovascular endpoint showed a relative risk reduction of 44% [hazard ratio 0.56 (95% CI, 0.46–0.69)]. 5644 (32%) of participants were older than 70 years making this by far the most representative primary prevention data of the benefits of statin treatment in the elderly.

Heart failure is common in the elderly secondary to ischaemia, hypertension and cardiomyopathy. A number of statin trials have been conducted in populations with grade 2–3 heart failure after post hoc analyses of general CHD prevention trials suggested benefits in grade 1–2 disease.[33] The Controlled Rosuvastatin Multinational Study in Heart Failure CORONA[34] and GISSI-Heart Failure (GISSI-HF)[35] studies showed no benefits of adding statin therapy in advanced heart failure but also that these drugs were not toxic in these populations.

Specific prescribing points in the elderly

Data from the large trials shows little difference in side-effect rates between statin and placebo arms.[36,37] However, many patients recruited to the trials have previous experience of statins and the designs of many trials incorporate an active run-in period in which those who suffer side effects are identified early. Thus side-effect rates may be underestimated especially in elderly populations. No specific dose reduction is advised or necessary for the elderly with statins though many general practitioners worldwide initiate therapy at low doses but unfortunately do not titrate the dose to efficacious levels resulting in a persistent under-treatment of lipids in the elderly. Drug interactions vary between compounds in the statin class. The most significant interaction is of cytochrome P450 3A4 metabolized statins (lovastatin, simvastatin, atorvastatin) with other drugs metabolized by this pathway – conazole antifungals, erythromycin, and in specialist practice, cyclosporine and HIV protease inhibitors (Table 38.2). Simvastatin interacts with amiodarone at doses >20 mg and other statins should be used if amiodarone therapy is necessary (e.g. for atrial fibrillation). A weaker interaction 3A4 can occur with diltiazem through this pathway but is not usually clinically significant. Drug interactions of this type are less significant for the other statins.

All statins frequently cause gastrointestinal disturbance by a transient dysregulation of bile acid metabolism through the farnesoid-X receptor pathway. This problem may be exacerbated in patients with diverticulosis or irritable bowel disease. Gastrointestinal side effects may be accompanied by a transient increase in bilirubin and transaminases. This problem is usually self-limiting within 2–3 weeks and on repeat measurement liver profiles have usually normalized.

Myalgia occurs in 5% of patients with statin therapy and is not associated with any change in CK.[37] Again often it is self-limiting but if symptoms persist than the statin therapy should be changed to the weaker agents that show predictably better side-effect profiles (pravastatin, fluvastatin). Myositis (raised CK, muscle pain) and rhabdomyolysis (CK > 20 × ULN; muscle pain; myoglobinuria) are rare side effects of statin therapy. The risk factors for rhabdomyolysis are age, creatinine, muscle mass, female sex, hypothyroidism and concomitant therapy with drugs interacting through the relevant cytochrome pathway (usually 3A4); likely to displace statins from plasma proteins; or sharing a myopathic tendency (e.g. other lipid-lowering drugs).

Ezetimibe

The cholesterol absorption inhibitor, ezetimibe, works by reducing the upper intestinal cholesterol absorption to produce in monotherapy around 20% reduction in LDL-C. This drug has proven to be very successful in the market due to its low side-effect profile with its main benefit being add-on therapy to statins to achieve targets.[38] Currently no CVD outcomes data is available on ezetimibe and the importance of this has recently been highlighted.[39] The Simvastatin-Ezetimibe in Aortic Stenosis trial[40] investigated the efficacy of a simvastatin–ezetimibe combination in 1873 patients with aortic stenosis – a common disease in the elderly. No benefit was shown on the combined valve disease-CVD events primary outcome or on valve progression-related endpoints, though a 20% reduction was seen in cardiovascular events. The data in advanced aortic stenosis from SEAS parallels that from other surrogate outcome trials. The Study of Heart And Renal Protection (SHARP) trial investigated the efficacy of simvastatin 20 mg and ezetimibe in 9270 patients with chronic renal failure including those on dialysis and showed a 17% reduction in cardiovascular events.[41]

An ongoing trial namely, IMPROVE-IT (the Improved Reduction of Outcomes: Vytorin Efficacy International Trial), in which simvastatin plus ezetimibe is compared with simvastatin plus placebo, is underway in a middle-aged population with acute coronary syndromes. This study will hopefully provide answers with respect to the benefits of ezetimibe monotherapy on CVD outcomes.

Bile acid sequestrants

Bile acid sequestrants reduce cholesterol absorption and reduce LDL-C by 15–20%. They can be used in monotherapy or combination therapy with any lipid-lowering drug except ezetimibe. They may raise TG levels and have modest positive effects on levels of HDL-C. They are not often used in the elderly as gastrointestinal side effects are common and interact with irritable bowel syndrome and diverticulitis to cause bloating, diarrhoea and constipation. Endpoint evidence exists for bile acid sequestrants from the Lipid Research Clinics trial where they reduced coronary events by 15%.[42]

Bile acid sequestrants have multiple drug interactions as they interfere with the absorption of all lipid-soluble drugs. A four-hour clear interval is recommended between taking these drugs and taking any other medication. Bile acid sequestrants cause gastrointestinal disturbance in 40% of patients. This may be accompanied by a liver-X-receptor (LXR)-induced hypertriglyceridaemia. Myalgia, myositis (raised CK, muscle pain) and rhabdomyolysis (CK > 20 × ULN; muscle pain; myoglobinuria) are rare side effects of bile acid sequestrant therapy and usually occur when it is prescribed with a concomitant statin.

Intervention on triglycerides

Several meta-analyses have found that TGs are an independent risk factor for CHD.[43,44] Raised serum TG levels (>1.7 mmol l^{-1}) are associated with abnormal

lipoprotein metabolism giving rise to increased atherogenicity. The lipid triad of high TG, low HDL-C and increased atherogenic particle numbers (high apo B, low apo A-1 concentrations) is associated with the metabolic syndrome found in many patients with obesity, insulin resistance, or diabetes mellitus. Highly elevated TG levels (>9–10 mmol l^{-1}) are a risk factor for pancreatitis.[45]

No specific trials have addressed hypertriglyceridaemia and most exclude patients with this condition. Thus there is no clear consensus on the benefits of directly targeting hypertriglyceridaemia in order to reduce CVD risk. Three drug classes are commonly prescribed for hypertriglyceridaemia namely: fibrates, niacin and omega-3 fatty acids. Statin therapy is still recommended first line for TGs <4.6 mmol l^{-1} as statins reduce TGs in direct proportion to their efficacy on LDL-C and the baseline TG level.[46] At higher TG levels fibrates and niacin are more efficacious and are recommended first-line therapies.[18,47] Guidelines suggest TGs are viewed as risk indicators for intensifying LDL-C-reducing therapy commonly stating an indication with a residual TG >2.3 mmol l^{-1} after initial statin therapy.

Fibrates

Fibrates are used to lower TG and raise HDL-C though their principal action is to increase lipoprotein particle sizes (which is well marked by TG). They reduce TG by 30–50%, raise HDL-C by 2–15% and reduce LDL-C by 0–10% depending on the drug and dose. Four drugs are available (Table 38.1). The evidence base for fibrates is contradictory.[48] The World Health Organization clofibrate trial[49,50] showed decreased cardiovascular events but an increase in total mortality due mostly to an excess of pancreatitis/cholecystitis. Later fibrate trials with gemfibrozil in primary prevention (Helsinki Heart Study)[51] and in secondary prevention patients with low HDL-C (<0.95 mmol l^{-1}) (Veterans Administration-HDL Intervention Trial)[52] showed reductions in cardiovascular events. Data with bezafibrate in the Bezafibrate Infarct Prevention (BIP) study[53] showed a non-significant slight reduction in events concentrated in a high triglyceride group (>2.3 mmol l^{-1}) though this was not reproduced in the patients with peripheral vascular disease in the Northwick Park Study. Fenofibrate reduced CHD events non-significantly and CVD significantly by 11% in patients with type 2 diabetes in the Fenofibrate Intervention in Event Lowering in Diabetes (FIELD) study.[54] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study also in 5518 patients with type 2 diabetes of fenofibrate added to baseline statin therapy showed a non-significant 8% reduction in CHD events with combination therapy which was, however, safe.[55] A subgroup hinted at a benefit in patients with TG >2.3 mmol l^{-1} and HDL-C <0.88 mmol l^{-1}. Meta-analyses of fibrate trials tend to suggest they are beneficial delivering a 11% reduction in CVD events mostly in smaller non-fatal events in all age groups but at the price of increases in cholecystititis, deep venous thrombosis and pulmonary embolism.[56,57]

Specific prescribing points

No specific dose reduction is advised or necessary for the elderly with fibrates. Fibrate therapy needs to be used with caution in patients with creatinine >150 μmol l^{-1}

Table 38.1 Notable statin trials.

Year	1994	1995	1996	2002	2002	2004	2008
Study	4S	WOSCOPS	CARE	HPS	PROSPER	CARDS	JUPITER
Setting	secondary prevention	primary prevention	secondary prevention	combined	combined	type 2 diabetes	primary prevention
Statin	Simvastatin	Pravastatin	Pravastatin	Simvastatin	Pravastatin	Atorvastatin	Rosuvastatin
Number patients	4444	6595	4159	20 536	5804	2838	17 802
Diabetes	202 (4.5%)	76 (1%)	586 (14%)	5963 (29%)	623 (11%)	2838 (100%)	(0) 0%
Follow-up (mean)	5.4 years	4.9 years	5 years	5 years	3.2 years	3.9 years	1.9 years
LDL-C lowering	36%	26%	28%	31%	34%	40%	50%
Age range (yrs)	35–70	45–64	21–75	40–80	70–82	40–75	60–71
>65 years	23%	0%	31%	52%	100%	40%	32%[a]
Primary endpoint	Total mortality 12% → 8%	CHD death/ non-fatal MI 8% → 5.5%	CHD death/ non-fatal MI 13% → 10%	Total mortality 15% → 13%	CHD death/ non-fatal MI and stroke 16% → 14%	CHD event or stroke 9% → 6%	CHD event or stroke 1.8% → 0.9%

4S, Scandinavian Simvastatin Survival Study; WOSCOPS, West of Scotland Coronary Prevention Study; CARE[20]. Cholesterol and Recurrent Events; HPS, Heart protection study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; CARDS, Collaborative Atorvastatin Diabetes Study; JUPITER, **J**ustification for the **U**se of statins **I**n prevention: an intervention **T**rial **E**valuating **R**osuvastatin

[a]Percentage of subjects older than 70 years

(eGFR $< 30\,ml\,min^{-1}$) as these drugs are renally cleared. Atrial fibrillation is common in elderly patients and guidelines recommend the use of warfarin for stroke prevention. Fibrates show a significant interaction with warfarin such that warfarin doses need to be decreased by 33%. Fibrates can interact with other lipid-lowering therapies to increase the risk of rhabdomyolysis. This is a particular problem with gemfibrozil which has a unique mechanism of glucuronidation and this causes increases in free statin acid concentrations (lovastatin, simvastatin) as well as causing problems with other drugs (e.g. pioglitazone). Gemfibrozil is not recommended to be used in combination therapy (especially statins) for any lipid disorder.[58,59]

Omega-3 fatty acids

Omega-3 fatty acids reduce TG by 20–25% at high doses.[60] The active components are docosahexaenoic acid (DHA) and eicosapentenoic acid (EPA). Epidemiological studies show a progressive reduction in events with fish intake, the greatest effects being seen with minimal intake as opposed to none.[61,62] At moderate doses omega-3 fatty acids have proportionally lesser effects but seem to reduce cardiovascular events especially sudden cardiac death. They can be used in monotherapy or combination therapy with any lipid-lowering drug. The endpoint evidence with omega-3 fatty acids is controversial. In the GISSI-Prevention study (DHA/EPA)[63] and DART-1 (fish oil capsules) studies they reduced CHD events by 13–25% but in the DART-2 study an increase in CVD events was seen. More recently in the Japanese Eicosapentaenoic Lipid Intervention Study (JELIS)[64] 1 g EPA reduced CVD events by 22% in a predominantly female, mostly primary prevention Japanese population with raised LDL-C and a high fish intake. The benefits, however, were concentrated in men and those with prior CHD. The second arm of the GISSI heart failure trial (GISSI-HF)[65] in grade 2–3 heart failure showed that 1 g EPA reduced cardiovascular events and death or heart failure admission by 9% with a number need to treat of 44.

Specific prescribing points

Omega-3 fatty acids have few significant drug interactions but can cause gastrointestinal disturbance and bloating. They may be associated with weight gain if given in preparations that require taking multiple capsules – usually less pure forms of DHA-EPA.

HDL-cholesterol

The inverse relationship between HDL-C levels and atherosclerotic CVD provides the epidemiological basis for the widely accepted hypothesis that HDL is atheroprotective. Based on this epidemiological data, HDL-C measurement forms part of routine CVD risk prediction tools. However, the biology of HDL is more complex than LDL and a single measurement is not necessarily a guide to HDL fluxes. Thus some HDL-raising therapies such as hormone replacement therapy or with a specific cholesterol ester transfer protein inhibitor (CETPi) (torcetrapib) have not reduced CVD events but showed increases while others associated with reduced HDL levels (e.g. apo A1 Milano infusion) show decreases in atheroma burden. The meta-analyses of HDL do show some benefits but rely heavily on the niacin trials as other agents have modest effects.[66] Guidelines are disparate when it comes to treatment targets for HDL-C. An international consensus exists that HDL-C should be $>1\,mmol\,l^{-1}$.[67] International guidelines state that low HDL-C is in indicator of increased CVD risk but argue that there is no specific treatment for HDL-C as it is only altered modestly, and not independently of changes in other lipid parameters, in the clinical trials.

Niacin

Nicotinic acid (niacin) is used to raise HDL-C and reduce TG. It raises HDL-C by 10–25%, reduces TG by 20–40%, and reduces LDL-C by 10–20% depending on the dose. It can also reduce lipoprotein (a) levels by 10–25%.[68] There is endpoint evidence when the immediate release formulation used a 3 g/day in the Coronary Drug Project where it reduced CHD events by 22%.[69] In subsequent studies niacin added to statins reduced rates of atherosclerosis progression in coronary (HDL Atherosclerosis Treatment Study; HATS)[70] and carotid arteries (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ARBITER-2)[71] even compared to ezetimibe (ARBITER-6).[72] Endpoint studies of niacin added to optimized LDL-C-lowering therapies are underway in patients with dyslipidaemia and CHD (AIM-HIGH)[73] or mixed secondary prevention and diabetes population (Heart Protection Study-2; treatment of HDL to reduce the incidence of cardiovascular events; HPS2-THRIVE[74]). In the underpowered AIM-HIGH study no benefit was seen with adding niacin to statin on CVD events in patients optimized to LDL-C $< 2\,mmol\,L^{-1}$ both prior to and post-randomization.[73] Given the problems with flushing with the immediate release form a modified release formulation (up to 2 g per day) or one co-formulated with the prostaglandin D2 type 1 receptor antagonist flush suppressant (laropiprant) are commonly used these days. These have similar lipid-lowering efficacy but lesser rates of flushing compared to immediate release niacin.

Specific prescribing points

No specific dose reduction is advised or necessary for the elderly with niacin. Niacin needs to be used with caution in

Table 38.2 Practical therapeutics of lipid-lowering drugs.

DRUG	Start dose	Usual dose	Pharmaco-kinetics	Metabolism	Important interactions	Important adverse events	Other tips
Atorvastatin	10 mg	20 mg (10–80)	Y $t_{1/2} = 14$ hrs E $t_{1/2} > 16$ hrs AUC +30%	CYP3A4	Conazoles Erythromycin Ciclosporin	GI disturbance Myalgia-myositis-rhabdomyolysis	
Fluvastatin	80 mg	80 mg (20–80)	Y $t_{1/2} = 0.6$ hrs E $t_{1/2} = 0.6$ hrs AUC – nil	CYP2C9	Nil	GI disturbance Myalgia-myositis-rhabdomyolysis	
Lovastatin	40 mg	80 mg (20–80)	Y $t_{1/2} = 3$ hrs E $t_{1/2} > 3$ hrs AUC +45%	CYP3A4	Conazoles Erythromycin Ciclosporin	GI disturbance Myalgia-myositis-rhabdomyolysis	
Pravastatin	40 mg	40 mg (10–40)	Y $t_{1/2} = 2$ hrs E $t_{1/2} > 2$ hrs AUC +19–27%	$3-\alpha$-isomer	Nil	GI disturbance Myalgia-myositis-rhabdomyolysis	
Rosuvastatin	10 mg	10 mg (10–20)[40]	Y $t_{1/2} = 19$ hrs E $t_{1/2} = 19$ hrs AUC – nil	CYP2C19 (10%)	Nil	GI disturbance Myalgia-myositis-rhabdomyolysis	
Simvastatin	40 mg	40 mg (10–80 mg)	Y $t_{1/2}$ 1.9 hrs E $t_{1/2} - 3$ hrs AUC +45%	CYP3A4	Conazoles Erythromycin Amiodarone Ciclosporin	GI disturbance Myalgia-myositis-rhabdomyolysis	
Bezafibrate	400 mg	400 mg	Y $t_{1/2} = 4$ hrs E $t_{1/2} = 8$ hrs AUC +160%	Glucuronide	Warfarin Statins	GI disturbance, rash Myalgia-myositis-rhabdomyolysis	
Ciprofibrate	100 mg	100 mg	Y $t_{1/2} = 81$ hrs E $t_{1/2}$ = NA AUC = NA	Glucuronide	Warfarin Statins	GI disturbance, rash Myalgia-myositis-rhabdomyolysis	

(continued overleaf)

Table 38.2 (*continued*).

DRUG	Start dose	Usual dose	Pharmaco-kinetics	Metabolism	Important interactions	Important adverse events	Other tips
Fenofibrate	Various 122/160/ 200 mg	Various 122/145/160/ 200 mg (122–267)	Y $t_{1/2}$ = 20 hrs E $t_{1/2}$ > 20 hrs AUC +10%	Glucuronide UGT A2	Warfarin Statins	GI disturbance, rash Myalgia-myositis-rhabdomyolysis	
Gemfibrozil	300 mg bd	600 mg bd	Y $t_{1/2}$ = 3.0 hrs E $t_{1/2}$ = 3.0 hrs AUC +10%	Glucuronide UGT A1 & UGT A3 **NB. CYP 2C8 inhibitor**	Warfarin Statins	GI disturbance, rash Myalgia-myositis-rhabdomyolysis	Avoid with statin combination therapy
Nicotinic acid (Niacin)	375–500 mg	1000–2000 mg (500–2000)	Y $t_{1/2}$ = 0.5 hrs E $t_{1/2}$ = NA AUC = NA	10% nicotinuric acid	–	Flush, rash, hyperglycaemia Hypophosphataemia Gout	Reduce flush with aspirin/ indomethacin.
Ezetimibe	10 mg	10 mg	Y $t_{1/2}$ = 22 hrs E $t_{1/2}$ > 22 hrs AUC +200%	Glucuronide	Ciclosporin	GI disturbance, rash	Add to low dose statin in myalgia
MaxEPA	1 g	10 g	Y $t_{1/2}$ = NA E $t_{1/2}$ = NA	Beta-oxidation	–	Bloating, weight gain	–
Omacor	1 g	1–2 g	Y $t_{1/2}$ = N/A E $t_{1/2}$ = N/A	Beta-oxidation	–	Bloating	–

Y, Young; E, Elderly

patients with creatinine >150 μmol l^{-1} (eGFR<30 ml min^{-1}) as this drug is renally cleared. Niacin interacts with warfarin such that warfarin doses need to be decreased by 20%. It can interact with other lipid-lowering therapies to increase the risk of rhabdomyolysis but the effect is less than with statin or fibrate monotherapy. The principal side effect of nicotinic acid is facial flushing. This can extend beyond erythema to a burning sensation. Though spectacular this is not a serious side effect. It occurs in 80% of patients commencing niacin therapy and the frequency and intensity of flushes habituate with time. Flushing can be decreased by slow dose titration, concurrent aspirin therapy (150 mg) or by indomethacin (200 mg) except if laropiprant is used and by slowing absorption using a snack.

Niacin has variable effects on glycaemic control in diabetes.[75] In most patients it has no or a transient effect though in some patients increases of up to 1 mmol l^{-1} in glucose (0.5% in HbA1c) are seen. Transient increases in bilirubin and transaminases are rarer with nicotinic acid than with other lipid-lowering agents. Myalgia occurs in 0.1% of patients on niacin and is not associated with any change in CK. Again often it is self-limiting but if symptoms persist than the therapy should be changed to another drug class. Myositis (raised CK, muscle pain) and rhabdomyolysis (CK > × 20 ULN; muscle pain; myoglobinuria) are very rare side effects of niacin therapy. The risk factors for rhabdomyolysis are similar to those described for statins.

Patients older than 80 years

Very little trial evidence exists for individuals older than 80 years. Ever since the early landmark statin trials such as 4S, CARE and LIPID excluded patients older than 75 years (<70 years for 4S) there has been a paucity of data on the older elderly. The PROSPER trial, which was specifically designed to evaluate statin therapy in the elderly, included patients aged 70–82 years and the mean age was 75 years.[30] The majority of patients were, however, younger than 80 years. This randomized placebo-controlled trial extended the treatment strategy already employed to younger individuals at the time to older individuals and confirmed the suggested benefits from subgroup analysis of the earlier studies. The question of whether the elderly will benefit from primary statin intervention was answered by the recent JUPITER study where 5644 patients were aged >70 years.[32] These two recent studies confirm the benefit of statins in older individuals and suggest the benefit to those older than 80 years. A recent meta-analysis of 10 randomized controlled trials which assessed the benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors found that the benefits were similar irrespective of age group (younger vs. individuals older than 65 years).[23] Little compelling trial evidence for lipid lowering in individuals older than 80 years is therefore available. However, the data available in the elderly suggests that the benefit demonstrated should extend to those older than 80 years.

Conclusion

Any clinical treatment decision requires consideration of the benefit to risk ratio. As is the case with cardiovascular risk estimation, this remains an inexact science. Statins have revolutionized preventative cardiovascular medicine and their benefits are undisputed following primary and secondary intervention trials which have now included a significant proportion of older individuals. The initiation of lipid-lowering therapy needs to be considered in the context of other CVD risk factors as CVD is multifactorial in origin with clustering of risk factors that have a multiplicative effect on CVD risk. Therefore, total cardiovascular risk management which includes factors such as lifestyle modification and blood pressure management are required in order to maximize cardiovascular risk reduction. Modifying lipids is only one of the essential components of this approach. When deciding on a therapeutic treatment option, clinicians have to weigh up the envisaged benefits against the potential detriment. Clinical acumen is therefore paramount when making a treatment decision in the elderly as these factors need to be considered.

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CHAPTER 39

Hypotension

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Hypotension is classically defined as drop in systolic blood pressure (BP) below 90 mmHg, producing symptoms of hypoperfusion to various organs. Although generally accepted, this number is arbitrary and many people with sustained hypertension or the elderly may become symptomatic at higher BPs. The body's autoregulatory mechanism prevents a significant fall in BP so as to maintain adequate perfusion of vital organs and their proper functioning. Such compensations are very fast and individuals are generally asymptomatic. Symptoms may develop if the BP drops below the range of autoregulation or if there is a delay in initiation or disruption of the regulatory mechanism. Hypotension is significant only if associated with symptoms or in the presence of a secondary condition that, if not controlled, will worsen hypotension and produce symptoms.

Hypotension when symptomatic is never physiological and is always secondary to an underlying cause. Hypotension is associated with many conditions, such as hypovolaemia (secondary to haemorrhage, severe diarrhoea, etc.), sepsis, anaphylaxis, tachycardia, bradycardia, valvular abnormality, tamponade, myocardial ischaemia, cardiomyopathy, pulmonary embolism, pneumothorax, adrenal insufficiency or side effects/toxicity of drugs. Symptoms are related to reduced perfusion to various organs – brain (dizziness, lightheadedness, blurry vision, syncope); skin (cold extremities); heart (tachycardia, palpitations, angina); kidneys (low urine output, renal failure); or gut (nausea, vomiting) – in addition to a general feeling of lethargy and generalized weakness. Symptoms persist until the underlying causes are corrected. Although these causes can affect any age group, outcome is poorer in the elderly.

There are two conditions that classically affect the elderly population – post-prandial hypotension (PPH) and orthostatic hypotension (OH) – producing a symptomatic fall in BP after eating and standing, respectively. These are transient in nature, typically producing symptoms due to reduced cerebral perfusion – dizziness, lightheadedness, blurry vision, syncope. They rarely last long enough to produce angina or renal failure.

Post-exercise hypotension (PEH) is a transient condition usually seen in hypertensive patients after a bout of exercise.

Orthostatic hypotension

Definition

Orthostatic or postural hypotension (OH) was first described by Bradbury and Eggleston in 1925.[1] OH is diagnosed when there is a reduction of $\geq$20 mmHg in SBP or $\geq$10 mmHg in DBP within 3 min of standing or using an upright tilt table at an angle of at least 60° with or without symptoms.[2] Although the definition is based on a consensus statement and the figures are arbitrary, a more modest drop in BP associated with symptoms is equally important. Delayed orthostatic hypotension (DOH), seen in 54% of patients with OH, is defined as a sustained fall in BP occurring beyond 3 min of standing or an upright tilt table test.[3] Initial orthostatic hypotension (IOH) is defined as a transient decrease of $\geq$40 mmHg SBP and/or $\geq$20 mmHg DBP within 15 s after standing and is associated with symptoms of cerebral hypoperfusion.[4]

OH represents one end of the spectrum of disorders of cardiovascular dysregulation. The spectrum (Figure 39.1) extends from very low to very high BP. The majority of individuals with normal BP are in the middle. At the right end are hypertensive individuals who have elevated BP all the time. Labile hypertensive individuals with BP ranging from 120/80 to 140/90 occupy the borderland between hypertensive and normal population. Individuals on the right side are asymptomatic and are treated to prevent complications in the future. At the left extreme are the individuals with OH. Individuals with 'mild dysautonomias' span the region between the OH and normotensive groups and include people with postural tachycardia syndrome (POTS) and neurally mediated syncope (NMS). Individuals

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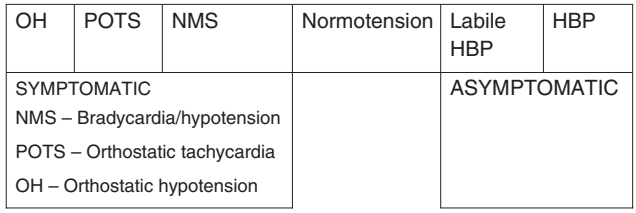

Figure 39.1 Cardiovascular dysregulation. HBP, high blood pressure; NMS, neurally mediated syncope; OH, orthostatic hypotension; POTS, postural tachycardia syndrome. Reproduced with permission from Robertson.[5]

with POTS have orthostatic tachycardia whereas those with NMS have normal pressures in all postures but occasionally have 'fainting' associated with a brief period (usually less than 1 min) of hypotension and/or bradycardia. Individuals on the left side have symptoms that affect quality of life and could be dangerous.[5]

Epidemiology

OH is a transient phenomenon with a high degree of intra-individual and intra-observer variability. OH is common among elderly populations with a varied prevalence of 6–34 % in community-dwelling people over 65 years of age[6–9] and around 20% among ambulatory nursing home residents.[10] Difference in measurement techniques of BP and timing of the measurement after change in position may contribute to the wide variations noted. The prevalence of OH increases with age from 14.8% in subjects aged 65–69 years to 26% in those 85 years and older. Differences in racial distribution have been documented by some, with predominance among whites,[11] whereas others documented no such difference.[12] The incidence of hospitalization secondary to OH increases with age and peaks over the age of 75 years at 233 per 100 000 patients. The median hospital stay is 3 days and the mortality rate is 0.9%.[13] OH is an independent predictor of 4 year all-cause mortality, with an age-adjusted relative risk of 1.8 [95% confidence interval (CI), 1.22–2.65].[14]

Many drugs have been implicated in either inducing or worsening of OH. These include antidepressants (tricyclic antidepressants, older monoamine oxidase inhibitors, serotonin–norepinephrine reuptake inhibitors), antipsychotics (phenothiazines), antihypertensives including diuretics,[15] narcotics and alcohol. Many factors have been linked with increased risk of OH (Table 39.1).

OH is highly prevalent in patients with Parkinson's disease (47%; range, 16–58%). Other neurological diseases with a high prevalence are pure autonomic failure (PAF) (33%), multiple system atrophy (MSA) (26%), idiopathic (autoimmune autonomic neuropathy) (17%) and diabetic autonomic neuropathy (14%). Among the diabetics, although the incidence of autonomic dysfunction is high (54% in type 1 and 73% in type 2), the prevalence of OH is not proportionate (8.4% in type 1 and 7.4% in type 2). OH increases the risk for coronary artery disease and all-cause mortality[17] and is associated with systolic hypertension and low body mass index,[18] stroke[19] and chronic kidney disease.[20]

Mechanism

The adoption of an upright posture by humans posed challenges for the BP regulatory system and through evolution the body developed mechanisms to accommodate the effects of gravity- and activity-mediated fluid shifts. Hormonal factors such as the renin–angiotensin–aldosterone system regulate BP over long periods. Cardiovascular regulation by the autonomic nervous system (ANS) prevents more than a 5–10 mmHg drop in SBP, increases DBP and increases the pulse rate by 10–25 beats per minute (bpm). Sympathetic autonomic dysfunction can result in the development of OH.

In normal individuals, upon standing, roughly 500–800 ml of blood is displaced from the upper part of body to the lower part, primarily to the abdomen and lower extremities. The drop in volume (~30%) reduces the venous return to the heart, leading to a drop in stroke volume and arterial pressure. This causes activation of two sets of pressure receptors: (a) high-pressure centres in the aortic arch and carotid sinuses and (b) low-pressure

Table 39.1 Factors linked with increased risk of orthostatic hypotension. Reproduced with permission from Hajjar.[16]

Physical and behavioural	Biochemical and humoral	Cardiovascular	Medications
Age	Hypokalaemia	Non-dipper status	Psychoactive medications
Low body mass index	Hyponatraemia	Postprandial hypotension	Vasodilators
Smoking	Changes in RAS	Supine elevated BP	Antiparkinsonians
Bed rest		Increased vascular stiffness	
		Decreased baroreceptor sensitivity	

receptors in the heart and lungs. These receptors, present in both the atrium and the ventricles of the heart, produce a tonic inhibitory effect on the sympathoexcitary neurons in cardiovascular areas of the medulla. A fall in venous return diminishes the stretch, decreasing their firing rates, thus resulting in increased sympathetic outflow. This causes a rise in BP by increasing systemic vascular resistance and constriction of splanchnic capacitance vessels. The baroreceptors located in the carotid sinus at the origin of the internal carotid artery transmit the local stretch signals to the nucleus tractus solitarius along the glossopharyngeal nerve. These receptors are responsible for an immediate increase in heart rate in response to the drop in carotid arterial pressure that occurs during an upright tilt test.[5] With ageing, the baroreceptor sensitivity and cardiovascular response to sympathetic stimulation are reduced, predisposing to OH.[14]

Prolonged orthostatic stress (20–30 min of standing) causes a substantial (20% in healthy adults) transcapillary filtration of the fluid shift from the blood into the interstitial space and causes additional peripheral pooling, thus decreasing venous return to the heart with a subsequent decline in BP and cardiac output. A progressive and sustained increase in muscle sympathetic nerve activity in response to prolonged orthostatic stress, together with the renin–angiotensin–aldosterone system, release of vasopressin and attenuation of atrial natriuretic factor, maintain cardiovascular homeostasis in the upright posture. This delayed OH is a consequence of one or more of the following: (a) increased peripheral venous pooling, (b) increased fluid transudation or (c) failure of the neural and humoral mechanisms.

Initial orthostatic hypotension (IOH) differs from typical OH in being transient, occurring immediately (within 15 s) upon standing, and is associated with a much greater fall in BP ($\geq$40 mmHg SBP and/or $\geq$20 mmHg DBP). This can be documented only by continuous beat-to-beat BP monitoring during active standing, hence passive tilt is of no diagnostic value. IOH is thought to be due to a mismatch between cardiac output and vascular resistance. The sudden contraction of the muscles in both the legs and the abdomen produces a compression of resistance and capacitance vessels and together with the local venoarteriolar axon reflex that constricts flow to skin muscle and adipose tissue increases the peripheral vascular resistance, thus causing an initial increase in venous return. The increase in right atrial pressure produces reflex-mediated lowering of the BP. Overcompensation drops BP to the orthostatic range. IOH explains the transient symptoms of cerebral hypoperfusion that develops after waking from an overnight sleep.[4]

Symptoms of OH occur more commonly in the mornings and after meals and is worsened by a hot bath or shower; sudden postural change, fever and alcohol consumption. It may be provoked by exercise, coughing, straining to defecate and hyperventilation. Symptoms are dependent not only on the absolute fall in BP but also on the rate of change and the ability of the cardiovasculature to autoregulate. Symptoms range from light headedness to syncope and include dizziness, weakness, blurry vision, neck pain, headache, angina, disturbed speech, confusion, impaired cognition, fall and syncope. OH is often one aspect of a more generalized disturbance in cardiovascular regulation. In the initial phase, patients tolerate the symptoms as the BP rises during the day. With progression of dysregulation, patients exhibit erratic swings of BP in response to various physiological and pharmacological stresses and develop supine hypertension by the end of the day which can cause nocturnal polyuria by pressure natriuresis.[21,22]

Causes of OH are broadly classified into acute and chronic (Table 39.2). Acute OH develops over a short duration, is more symptomatic and results from acute processes such as sepsis, dehydration or myocardial ischaemia. Chronic OH develops over a longer duration, is usually asymptomatic initially and is mostly secondary to central or peripheral nervous system diseases.[22]

Evaluation and diagnosis

A detailed history and physical examination can identify the cause in about 45% of patients with OH. One must include a comprehensive neurological assessment and look for the signs of other systemic disorders causing OH. To establish the diagnosis of OH, the first step is to determine BP and heart rate after the patient has been quietly supine for at least 5 min and again after 1 and 3 min of standing. If ambulatory BP monitoring is required, measurements before breakfast, after medication, after meals and before bed are most useful. Variations in heart rate in response to OH can provide clues to aetiology: absent or minimal cardio-acceleration (<10 bpm) suggest baroreflex impairment or defect in the autonomic nervous system, tachycardia (>20 bpm) indicates volume depletion and a drop in heart rate suggest vasovagal response.[22]

When symptoms are suggestive of OH but no obvious cause is identified, the patient's medications should be reviewed before other aetiologies are considered and potentially any causative medications should be discontinued if possible. If discontinuation of medication is not possible, consider treating OH pharmacologically. If the medication does not appear to be fully responsible for OH, check the volume status. If dehydrated, hydration may improve symptoms; if euvolumic, look for other non-neurogenic causes. Angina, dyspnoea and oedema suggest cardiac aetiology; vomiting, diarrhoea, burns and diuretic use suggest dehydration; fever may indicate sepsis or other infections. Once medication and non-neurogenic aetiologies have been ruled out, consider neurogenic causes of OH. They are difficult to diagnose and treat and a neurology

Table 39.2 Classification of orthostatic hypotension.

Acute		Chronic
Neurogenic		*Non-neurogenic*
Acute pandysautonomia		Ageing
Acute paraneoplastic autonomic neuropathy		Hypertension
Autoimmune autonomic ganglionopathy (AAG)		
Bezold–Jarisch reflex activation		*Central nervous system*
Botulism		Lewy body dementia
Carotid sinus syncope		Multiple sclerosis
Drug induced/toxic acute autonomic neuropathy		Multiple system atrophy (MSA)
Guillain–Barré syndrome		Myelopathy
Micturition syncope		Olivo-ponto-cerebellar atrophy
Porphyria		Parkinson's disease
		Posterior fossa tumours
Non-neurogenic		Spinal cord tumours
Adrenal crisis	Diarrhoea	Strokes
Anaemia	Haemorrhage	Subacute combined degeneration
Arrhythmias	Mastocytosis	Syringomyelia
Arteriovenous malformation	Myocardial infarction	Transverse myelitis
	Pheochromocytoma	
Burns	Pregnancy	*Peripheral nervous system*
Carcinoid	Sepsis	Alcoholic polyneuropathy
Carditis	Vomiting	Amyloidosis
Congestive heart failure		Autoimmune autonomic neuropathy
Dialysis		Diabetes mellitus
		Dopamine-b-hydroxylase deficiency
Drugs		Familial dysautonomia (Riley–Day syndrome)
ACE inhibitors	Insulin	HIV/AIDS
Alpha receptor blockers	Marijuana	
Barbiturates	Monoamine oxidase inhibitors	Nutritional deficiency (vitamin B_{12}, folate)
Beta-blockers	Nitrates	Paraneoplastic syndrome
Bromocriptine	Opiates	Pure autonomic failure (PAF)
Calcium-channel blockers	Phenothiazines	Tabes dorsalis
Diuretics	Sildenafil	Uraemia
Ethanol	Tricyclic antidepressants	Wernicke–Korsakoff syndrome
Hydralazine	Tizanidine	
	Vincristine	

consultation may be helpful. Laboratory tests should be directed to assist clinical diagnosis and may include haemoglobin, blood urea nitrogen and a creatinine level.[23]

Anhidrosis, miosis and reduced sphincter tone point to autonomic failure. Autonomic function tests are useful to evaluate autonomic disorder and response to therapy. Heart rate variations during deep breathing accesses the function of parasympathetic effect on the heart. Arrhythmia is measured by electrocardiograph with the patient lying supine during 1 min of slow and deep breathing with 5 s inspiration and 7 s expiration. Normally the ratio of the longest expiratory to shortest inspiratory R–R interval is >1.15. The cold pressor test assesses the function of sympathetic effects on BP in response to immersion of the hands in ice-cold water (4° C) for 1 min (Normal: rise of ≥15 mmHg in SBP or ≥10 mmHg in DBP). Age and medications may affect the response to these bedside tests. Other autonomic testing that can be performed includes the quantitative Valsalva manoeuvre, carotid sinus massage and cardiovascular sensitivity to tyramine, phenylephrine or isoproterenol. Measurement of supine and upright plasma levels of norepinephrine and vasopressin can distinguish central from peripheral causes of autonomic failure. In

central causes, the supine norepinephrine level is normal but fails to increase when posture becomes upright and vasopressin is low, whereas in peripheral causes the supine norepinephrine is low and vasopressin is normal.[21,22]

Severe OH with marked supine hypertension, modest gastrointestinal impairment, very low plasma norepinephrine level and no other neurological system involvement suggests pure autonomic failure (PAF). Some, but not all, patients with Parkinson's disease and autonomic failure have OH. Patients with dementia with Lewy bodies have visual hallucinations. Multiple system atrophy (MSA), the severest of dysautonomias, involves not only the autonomic but also the cerebellar and extrapyramidal systems. Magnetic resonance imaging (MRI) shows degenerative changes in putamen. Dopamine b-hydroxylase (DBH) converts dopamine to norepinephrine and the gene is located on chromosome 9q34. DBH deficiency is an extremely rare disorder. These patients have severe OH, exercise intolerance, ptosis and retrograde ejaculation. These patients lack norepinephrine in their neurons and instead have dopamine. They respond very well to droxidopa.[5]

Orthostatic hypertension

Some individuals have orthostatic hypertension, that is, an increase rather than a decrease in BP upon standing. More severely affected individuals have rare disorders such as baroreflex failure, mastocytosis, hyperadrenergic POTS or pheochromocytoma.[5]

Prevention and treatment of OH

The first step in the treatment of OH is diagnosis and management of underlying reversible causes such as anaemia and hypovolaemia. Non-pharmacological intervention is attempted before pharmacological treatment.

Non-pharmacological intervention[21,24]

1 Educating patient and family to avoid any potential aggravating factors such as heat and dehydration.

2 Increase intake of salt (10–20 g daily) and fluid (1.25–2.5 l daily) if there are no contraindications such as CHF.

3 Eat smaller and more frequent meals.

4 Avoid alcohol, prolonged standing, large meals, strenuous exercise, hyperventilation and straining during urination or defecation.

5 If possible, avoid medications known to cause OH.

6 Elevate the head end of bed while sleeping to reduce nocturia, supine hypertension and sudden pooling of blood when rising in the morning.

7 Rise slowly from supine to sitting to standing position.

8 Drinking two cups (500 ml) of water 30 min before rising will raise SBP >20 mmHg for 2 h.

9 Use compression stockings and an abdominal binder to minimize venous pooling.

10 Dorsiflex feet several times before standing.

11 For deconditioning – utilize exercise such as swimming or recumbent biking.

12 Physical counter-manoeuvres involve isometric contraction of muscles below the waist for 30 s at a time. Specific manoeuvres include toe raising, leg crossing and contraction, bending at the waist, leg elevation and slow marching in place.

Pharmacological treatment

When non-pharmacological interventions fail, medications should be tried to control the symptoms. The available medications are summarized below.

Fludrocortisone is a mineralocorticoid with minimal glucocorticoid effect. It expands blood volume by salt retention. The starting dose is 0.1 mg per day with increments of 0.1 mg every week until a maximum dose of 1 mg is reached or trace pedal oedema develops. Common side effects are headache, hypokalaemia, heart failure and supine hypertension.[22]

Midodrine (α_1-agonist), a prodrug, is converted into active desglymidodrine. It is well tolerated and increases the SBP by an average of 22 mmHg. It stimulates both arterial and venous systems without direct CNS or cardiac effects and does not increase heart rate. It is useful in PAF and diabetic neuropathy. The starting dose is 2.5 mg three times per day with increments of 2.5 mg weekly to a maximum dose of 10 mg three times per day. Side effects are piloerection, pruritus, urinary hesitancy and retention in males. This medication is contraindicated in patients with coronary heart disease, heart failure, urinary retention, thyrotoxicosis and acute renal failure[21]

DL- and L-dihydroxyphenylserine (DOPS) are synthetic, non-physiological, norepinephrine precursors that are decarboxylated by the ubiquitous L-amino acid decarboxylase to norepinephrine. Of the four stereoisomers, only L-*threo*-DOPS is pharmacologically active. Since the conversion of DOPS to norepinephrine bypasses the dopamine b-hydroxylation step of catecholamine synthesis, DOPS is the ideal therapeutic agent for patients with dopamine b-hydroxylase deficiency since such individuals are unable to synthesize norepinephrine and epinephrine in the central and peripheral nervous system. This agent may also be of benefit in patients with familial amyloid polyneuropathy, Parkinson's disease, multiple system atrophy and pure autonomic failure.[25]

Pyridostigmine is a cholinesterase inhibitor. As it improves ganglionic neurotransmission in the sympathetic baroreflex pathway that is activated during standing, it improves OH without worsening supine hypertension. The starting dose is 30 mg two or three times per day and the maximum dose is 60 mg three times per day. Common side effects are abdominal colic and diarrhoea.[24]

Recombinant human erythropoietin increases BP by 10 mmHg and improves orthostatic tolerance, especially dizziness in patients with anaemia that often occurs in autonomic failure. The mechanism of increase in BP, although unknown, is not believed to be due to an increase in blood volume or viscosity. The dose is 25–75 U kg^{-1} subcutaneously three times per week. It is well tolerated.[21]

NSAIDs (non-steroidal anti-inflammatory drugs) are added to fludrocortisones to control smooth muscle relaxation and to increase peripheral resistance. They possibly work by inhibiting prostaglandin synthesis, particularly prostaglandin E. The indomethacin dose is 75–100 mg per day. Side effects include gastrointestinal toxicity, renal toxicity and worsening of heart failure.[26]

Indications for referral to a specialist

Geriatric consultation should be sought for frail elderly patients and those with multiple comorbid conditions. A cardiology referral is indicated for uncontrolled supine hypertension, severe heart failure and recent arrhythmia. A neurologist can be consulted for specialized autonomic testing or progressive autonomic failure.[22]

Postprandial hypotension

Definition

A postprandial fall in BP was first observed and reported in 1935 by Gladstone in a hypertensive patient and in 1953 by Smirk in patients with autonomic failure. Kjartan Seyer-Hansen in 1977 recognized postprandial hypotension as a clinical problem in a patient with Parkinson's disease.[27,28]

Epidemiology

Postprandial hypotension (PPH) is defined as a drop in systolic BP of ≥20 mmHg within 2 h after a meal or a drop of SBP from ≥100 mmHg pre-meal to below 90 mmHg within 2 h after a meal.[28]

PPH is common in elderly individuals. The prevalence of PPH varies depending on the risk group: 24–36% among nursing home residents, 50% in elderly patients with syncope and 67% in hospitalized geriatric patients. The prevalence is higher in elderly patients with autonomic failure, diabetes mellitus, hypertension, Parkinson's disease and end-stage renal disease on dialysis.[29] Hypertensive patients with PPH have a higher prevalence of asymptomatic cerebrovascular damage than those without PPH (83 versus 44%), as evidenced by a higher number of lacunae and leukoaraiosis on MRI of the brain.[30] PPH is associated with a higher incidence of falls, syncope, new coronary events, new stroke and total mortality in the elderly population.[31] PPH is not associated with OH but the two can be additive.[32]

Risk factors

Although the aetiology of PPH is poorly defined, various risk factors have been identified that influence the magnitude of a postprandial fall in BP. These include meal composition, temperature, volume and time of meal ingestion, medications and illnesses affecting autonomic nerve function.

In healthy elders, isocaloric and isovolaemic intraduodenal infusion of glucose, fat and protein reduce SBP and increase heart rate and splanchnic blood flow by similar magnitudes but the onset is earlier with glucose. The slowing of gastric emptying and the stimulation of gastrointestinal hormone release by oral fat and protein are mediated by fatty acids and amino acids, respectively. This could be the possible reason for the relative latency in the response. A warm (50° C) meal but not cold (5° C) reduces postprandial BP. Medications, especially psychotropic, cardiovascular and diuretic drugs, when administered with a meal can potentiate PPH.[31,33–35]

Pathophysiology

Age-related illness and unhealthy ageing cause PPH. The pathophysiology of PPH is poorly understood and is multifactorial. Factors include splanchnic blood flow, gastric distension, small intestinal nutrient delivery and neural and hormonal mechanisms.

PPH appears to be secondary to inadequate cardiovascular adjustment for the normal postprandial reduction in BP. Following a meal there is a doubling of superior mesenteric arterial flow. In healthy adults, BP is maintained by an increase in heart rate, forearm vascular resistance, cardiac index and sympathetic activity. Patients with PPH develop a postprandial decline in BP and systemic vascular resistance without a change in forearm vascular resistance, reduction in left ventricular end diastolic volume and poor sympathetic response.[36] Also, in healthy adults, gastric distension attenuates PPH by increasing BP and heart rate – 'gastrovascular reflex'. This reflex is reduced in elderly people with PPH. Muscle nerve sympathetic activity response to an oral glucose load and heart rate spectral analysis showed a blunted increase in sympathetic activity associated with the intake of a meal in elderly patients with PPH compared with young adults. A 200% increase in sympathetic activity would be needed to prevent PPH.[29]

The nitric oxide (NO) synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) attenuated PPH with

minimal effect on gastric emptying, suggesting the role of NO in development of PPH.[37]

Various vasoactive peptides released from the small intestine in response to the ingestion of food have been implicated in PPH and include calcitonin gene-related peptide (CGRP) and glucagon-like peptide-1 (GLP-1). CGRP levels increase following a meal and this increase is associated with the reduction of BP and pathogenesis of postprandial hypotension.[38] GLP-1 released from 'L-cells' in the small intestine is associated with acarbose in attenuation of hypotensive response to sucrose and slows gastric emptying.[39] Failure of intravenous glucose, a potent stimulus to insulin secretion, to affect BP in the elderly and that PPH occurs in patients with type 1 diabetes, who are by definition insulin deficient; argue against the major role of insulin in PPH. Plasma levels of VIP and substance-P, known vasodilators, are not affected by oral glucose.

Clinical features and diagnosis

Symptoms of PPH are due to cerebral hypoperfusion and manifest as dizziness, light-headedness, weakness, fall or syncope after a meal. Patients may sometimes present with chest pain or dyspnoea. PPH is suspected in any elderly person presenting with the above complaints especially in patients with autonomic failure, diabetes mellitus, Parkinson's disease or end-stage renal disease. Ambulatory BP can be monitored to include a major meal along with continued BP monitoring for at least 2 h after the meal. In admitted patients, measuring BP every 10 min starting 15 min before until 60 min after finishing breakfast utilizing a sphygmomanometer can detect about 70% of patients with PPH. This has been suggested by some as a practical and patient-friendly way to diagnose PPH.[40]

Treatment

Non-pharmacological interventions

1 Education of patients about the risk of falling after meals.
2 Lie recumbent and avoid a prolonged sitting or standing posture after meals.
3 Discontinue potential medication.
4 Drink water before meals.
5 Reduce carbohydrate consumption.
6 Eat smaller, more frequent meals.
7 Liberal salt and water intake.
8 Avoid alcoholic beverages.

Pharmacological treatment[28,29,39,41]

Acarbose, caffeine, guar and octreotide are the most frequently used medications for PPH.

Caffeine, an adenosine receptor antagonist, may ameliorate PPH. Dosage is individualized and can be titrated from 60 to 200 mg orally before meals.

Guar gum is derived from the guar bean and acts as a bulking agent. It prevents PPH by slowing glucose absorption. The dose is 4 g orally before meals. Side effects include abdominal pain, diarrhoea and flatulence.

Octreotide, a somatostatin analogue, reduces PPH most likely by increasing splanchnic and peripheral vascular resistance. The dose is a 50μg subcutaneous injection 30 min before meals. Side effects include abdominal pain, QT prolongation and pain at injection site.

Other medications that have been evaluated for treatment include the combination of denopamine (a β_1-agonist) and midodrine (but not as monotherapy); vasopressin and indomethacin for attenuation of PPH. Cimetidine, dihydroergotamine and diphenhydramine failed to show an effect on PPH.

α-Glucosidase inhibitors such as acarbose, voglibose and miglitol act by inhibiting carbohydrate digestion at the level of the brush border in the small intestine. Their effect is secondary to alterations in circulating vasodilators and gut peptides secretion. Specifically, an increase in glucagon-like peptide I is thought to slow gastric emptying, thus inhibiting PPH. The dose is 100 mg of acarbose or 200μg of voglibose orally before meals. Miglitol can be used at 25 mg with the first bite of the meal. Side effects include diarrhoea and flatulence.

Post-exercise hypotension (PEH)

In 1897, Hill documented PEH during the 90 min following a 400 yard dash.[42] In 1971, Groom reported a consistent decrease in systolic and diastolic BP in runners immediately after running at an estimated speed of 6 mph for more than 4 h.[43] It was only after Fitzgerald's report in 1981 of a personal observation that jogging for 25 min decreased labile pressure to near normal levels that lasted for several hours[44] that the phenomenon of PEH gained importance as a clinical entity.

Definition

Post-exercise hypotension (PEH) is a term used to describe the transient reduction in BP following an acute bout of exercise. There are no defined criteria for the magnitude and duration of this decrease in BP post-exercise to diagnose PEH. Eliciting the phenomenon of PEH by electrical stimulation of muscles instead of actual exercise is called post-stimulation hypotension (PSH).[45]

Epidemiology

PEH has been observed in young and middle-aged normotensive people and with patients with borderline and established essential hypertension. PEH lacks gender specificity and occurs in both men and women. PEH does not appear to be correlated with exercise intensity or duration or the amount of exercising muscle mass. The nadir of the PEH response generally occurs within the first 60–70 min of recovery. The average drop in BP in patients with essential hypertension varied from (systolic/diastolic) 11/4 mmHg in 30–90 min post-exercise to 9/4 mmHg between 2 and 3 h to an average of 2.8/1.7 mmHg over 24 h. The average drop in borderline hypertensive patients was 14/9 mmHg and in normotensive patients it was 8/9 mmHg.[45–47] Diurnal variations have been observed in PEH, which is less marked in the morning, probably because the exercise-mediated decrease in peripheral resistance is not as apparent at this time of day.[48]

Although PEH occurs in both normotensive and hypertensive individuals after either resistance or endurance exercise, it is more predictive in hypertensive individuals.[46] In the healthy normotensive population, chronic exercise leads to structural vascular changes that include increased arterial luminal diameter and compliance. Older hypertensive individuals are resistant to alteration due to replacement of elastic fibres by collagen and calcium. PEH also occurs in endurance-trained individuals, probably due to reduced cardiac output. In sedentary men PEH is secondary to vasodilatation, suggesting that exercise training may alter the mechanism but not the magnitude of PEH. As PEH is a function of baseline BP, the magnitude of the fall is expected to be more in hypertensive individuals. The magnitude diminishes with exercise-induced reduction in baseline BP. About 25% of hypertensive individuals called 'non-responders' do not appear to sustain BP reductions after endurance training, suggesting a genetic role in PEH. Meta-analysis of longitudinal studies showed no influence of frequency or intensity of exercise training programmes on the BP-lowering effect.[49]

PEH and initial OH are not predictors of syncope post-exercise even though the inability to maintain BP is a crucial factor.

Syncope post-exercise is a phenomenon seen exclusively after prolonged exercise (~4 h). PEH is seen even after short bouts of exercise and the magnitude is unrelated to the duration of exercise, thus indicating the role of other factors involved in post-exercise syncope.[50]

Clinical implications

If PEH is of sufficient magnitude, it could be sustained and evoked under conditions of normal daily living. Then regular periodic exercise can potentially become a non-pharmacological tool in the management of hypertension. Although some studies have shown a sufficient drop in BP and sustained effect, many others are contradictory. Further studies are needed to determine the dose, timing and type of exercise required for a sustained hypertensive effect.

Key points

- Hypotension is a major problem in older persons, leading to dizziness, falls, syncope, stroke, myocardial infarction and death.
- Orthostatic hypotension can occur immediately on standing or after a few minutes.
- Postprandial hypotension is due to an increase in the vasodilatory peptide calcitonin gene-related peptide.
- Postprandial hypotension can be treated with α_1-glucosidase inhibitors, which increase glucagon-like peptide-1.

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CHAPTER 40

Hypertension

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Definition and prevalence

Hypertension is a very prevalent disorder affecting about 1 billion people worldwide[1] and, as such, it is the most common modifiable risk factor for conditions such as atherosclerosis, stroke, heart failure, atrial fibrillation, diabetes mellitus, sudden cardiac death, acute aortic syndromes and chronic kidney failure and may cause death and disability in patients of all ages.[2]

It is thought to affect up to 70% of individuals over the age of 65 years. The exact prevalence of hypertension varies with the age, race and the overall health status of the population studied, and also the blood pressure cut-offs points used to define hypertension. Hypertension in elderly patients is a complex cardiovascular disorder that affects women more than men and occurs in essentially all races, ethnic groups and countries. Although it appears to be underdiagnosed in general and particularly among women, minorities and underserved populations, clearly it is also undertreated. Elderly persons are more likely to have hypertension and isolated systolic hypertension (ISH), target organ damage (left ventricular hypertrophy, renal impairment and albuminuria, hypertensive retinopathy) and clinical cardiovascular disease (CVD), to develop new cardiovascular (CV) events and are less likely to have hypertension controlled.

An international consensus exists about the limits of normal values for brachial blood pressure at 140/90 mmHg.[3] All define a blood pressure of 160/100 mmHg as requiring therapeutic intervention and 200/120 mmHg as very high risk requiring immediate management. There is less consensus on the cut-offs for blood pressure measured by other techniques. Many groups are now beginning to recommend the use of ambulatory blood pressure monitoring (ABPM) and the recent UK NICE guidelines have suggested that it has a primary role in the diagnosis of hypertension given its superior predictive value for CVD events compared with rather variable brachial measurements and its ability to counter stress-induced or 'white coat' hypertension.[4]

The US guidelines[5] introduced the concept of pre-hypertension, representing a systolic blood pressure (SBP) of 120–139 mmHg or diastolic blood pressure (DBP)of 80–89 mmHg, previously classified as 'normal' or 'high normal' blood pressure. Other guidelines recognize pre-hypertension as a potential risk factor but stress the role of CVD risk assessment and risk calculation as the primary guide to a requirement for any intervention – lifestyle or therapeutic. Pre-hypertension was introduced, in part, on findings of the Framingham Heart Study (FHS) suggesting that normotensive individuals at age 55 years have a 90% lifetime risk of developing hypertension.[6]

The recommendation was based on the results of 30 worldwide clinical trials conducted in 1997 and a report estimating that the risk of cardiovascular mortality doubles with each 20/10 mmHg rise in blood pressure, starting at levels as low as 115/75 mmHg.[7] In addition, evidence has accumulated which classifies individuals with comorbidities and an SBP >130–139 mmHg as suboptimal. These conditions include heart failure and left ventricular dysfunction, diabetes mellitus, chronic kidney disease and established CVD conditions such as coronary artery disease (CAD), peripheral arterial disease (PAD) and carotid artery disease.

A long standing controversy exists about hypertension in the elderly and some argue that usual definitions of hypertension and target BP levels might not be applicable to the elderly hypertensive population. The higher prevalence of hypertension in the elderly partially reflects the increase in the prevalence of arterial stiffening and thus changes in reflection pressure wave timing. The new generation of hypertension diagnostic devices specifically measure pulse wave reflection, velocity and pulse amplification parameters. There is no consensus on target values or optimal measures for pulse wave diagnostics as yet although all

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studies show that either directly measured or inferred central blood pressures (ascending aortic arch) are better predictors of outcomes than brachial measurements. As this technology is not widely available, older measures of specific subtypes of hypertension are useful.

Pathophysiology

Blood pressure regulation is a complex process, subject to multiple interacting physiological systems, and also lifestyle and genetic factors. In its simplest conceptualization, the cardiovascular system is governed by Ohm's law, which, when adapted to a haemodynamic system, states that flow (Q) is proportional to the pressure gradient (ΔP) and inversely proportional to the resistance (R) across a conduit.

In terms of the cardiovascular system, BP is the product of cardiac output and vascular resistance. Since cardiac output does not increase with age, hypertension in the elderly is, to a large extent, a result of increased vascular resistance. In combined systolic and diastolic hypertension (SDH), the problem arises at the site of the resistance arterioles, the smaller muscular vessels where 80–90% of arterial resistance occurs. Increased constriction at this level affects both SBP and DBP. In contrast, ISH develops as a result of large arteries that have become less compliant and therefore less able to accommodate volume changes. In young normotensive individuals, large elastic vessels contribute little resistance to blood flow. During systole, the aorta and other large arteries expand to accommodate the stroke volume, which attenuates the rise in intra-arterial pressure. During early diastole, elastic recoil of large arteries sustains forward flow, augmenting the DBP despite runoff into arterial branches. Age-related loss of elasticity increases vascular impedance, resulting in a more rapid rise in blood pressure during systole and to a higher level. The higher peak pressure, coupled with diminished elastic recoil, results in rapid runoff to the periphery, resulting in lower DBP (Figure 40.1). A low DBP is not entirely benign. Since myocardial perfusion occurs during diastole, diastolic hypotension may result in subendocardial ischaemia. While other constituents no doubt factor into the pathogenesis of hypertension, age-related loss of arterial elasticity successfully predicts widening of the pulse pressure (PP), ISH and the plateau in DBP that develop with ageing. Figure 40.1 depicts these changes over the course of a single cardiac cycle. Ageing blood vessels undergo a host of structural and functional changes, resulting in decreased compliance and increased resistance to flow. These changes particularly affect the intima and media of large arteries. With age, elastic fibres progressively decrease in number and elasticity and the collagen matrix increases. This fibrous transformation results in arteriosclerosis and is compounded by calcification and an increase in the number and size of

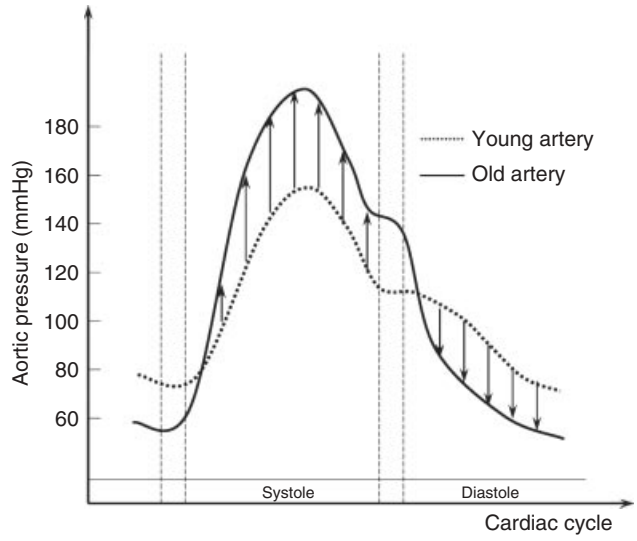

Figure 40.1 Blood pressure changes in an old versus a young artery during a cardiac cycle. The arrows indicate increased pressure during systole and decreased pressure during diastole that older arteries experience due to arteriosclerosis.

vascular smooth muscle cell. The combined effect is a fall in the total cross-sectional area of peripheral vasculature. Furthermore, the dynamic nature of endothelial-derived vasoactive substances that control vascular tone is also affected by age. The delicate balance between vasoconstricting agents (such as endothelin and angiotensin II) and vasodilating agents (such as prostacyclin and nitric oxide) is offset. Nitric oxide (NO), previously termed endothelial-derived relaxing factor (EDRF), is a potent vasodilator that has been extensively studied. An age-associated decline in NO-mediated vasodilatation has been demonstrated.[8] A decreased secretion of NO and also a blunted response to NO have further been documented. Endothelial dysfunction, possibly as a direct effect of elevated peak pressure, inhibits secretion of these compounds.[9] It remains unclear to what extent the imbalance of endothelial-derived vasoactive compounds is a cause or effect of high blood pressure, but impairment of effective vasodilator agents, in the absence of appropriate compensatory mechanisms, will result in increased vascular resistance. The endothelium also secretes a number of factors that act on smooth muscles in an autocrine manner. These include interleukin-1 and insulin-like growth factor. *In vitro*, these influence the migration and proliferation of smooth muscle cells, which in turn increase vascular rigidity and decrease lumen size.

Despite increased levels of serum norepinephrine that occur in the elderly, the role of the sympathetic nervous system in the pathogenesis of hypertension appears to be more complex than mere overstimulation. The sympathetic nervous system has little clinical impact on older normotensive subjects, even with increased levels of

serum norepinephrine. This is due to decreased adrenergic receptor function. Downregulation of β-adrenergic inotropic, chronotropic and vasodilatory response, and also α-adrenergic vasoconstrictor response, has been documented in the elderly. With receptor downregulation in the face of increased norepinephrine release, α_1-adrenergic vascular tone is comparable in old and young normotensive subjects. It has been proposed by some experts that older hypertensive subjects have a relatively less degree of suppression of α_1-adrenergic relative to β_2-adrenergic activity[10] and age-related hypertension is in part due to diminishing β-mediated vasodilatation whereas α-mediated vasoconstriction continues relatively unabated. Similar findings have been observed in animal studies. Decreased carotid baroreceptor sensitivity and responsiveness occur with age. Consequently, a larger change in blood pressure is needed to trigger the appropriate compensatory response. The impaired reflex is manifested clinically as wide blood pressure fluctuations in the elderly compared with the young, and also increased susceptibility to clinically significant orthostatic hypotension and postprandial hypotension. The age-related baroreceptor reflex dysfunction is not necessarily limited to hypertensive persons alone, but decreased vascular distensibility at the carotid sinus, as seen in hypertensive subjects, is likely to play a central role in the process and many antihypertensive medications will further exacerbate the condition.

Ageing kidneys undergo multiple changes, which may affect blood pressure regulation. A sodium load is secreted less rapidly and less completely as renal function declines. Similarly, the elderly are more sensitive to free water depletion or repletion than the young. Angiotensin II promotes sodium reabsorption from the distal tubules directly and indirectly through aldosterone release and stimulation of the autonomic nervous system. The renin–aldosterone–angiotensin axis, however, is less responsive with age. There is a decrease in serum renin levels and activity, which may be the result of decreased functional glomeruli and a decrease in serum angiotensin II and aldosterone levels. The net effect of these changes is towards sodium retention. Free water retention ensues to maintain sodium homeostasis. It has been suggested that chronic extracellular volume expansion due to sodium and water retention leads to increased vascular resistance through the mechanism of autoregulation of organ blood flow. These observations are consistent with the high prevalence of salt sensitivity among older hypertensive individuals. Atrial natriuretic peptide (ANP) is released primarily from the atria in response to stretch due to volume overload. ANP acts both as a peripheral vasodilator and as a natriuretic/diuretic hormone. Brain natriuretic peptide (BNP) was initially identified in the brain but is also present in the ventricles. It is homologous to ANP and its serum concentration is normally approximately one-fifth that of ANP. In heart failure, levels of BNP can increase dramatically. A simple serum assay has been devised for the measurement of BNP and is now commonly used in the management of heart failure.

Several variants of ANP and related hormones have been identified. Of note is a hormone with a digitalis-like effect. This putative hormone appears to be ouabain or an isomer of ouabain and binds the digitalis receptor on the sodium potassium adenosine triphosphatase pump (Na-K-ATPase) in an inhibitory manner. This hormone differs from ANP in that it increases vascular resistance. A proposed mechanism is that the Na-K-ATPase inhibitor facilitates renal sodium excretion but also diminishes intracellular sodium release, resulting in increased concentrations of sodium in smooth muscle cells. Passive sodium–calcium exchange subsequently results in increased intracellular calcium and, therefore, vascular tone.[11,12] These mechanisms may explain the high incidence of salt sensitivity in subjects with essential hypertension, but more investigation is needed to determine fully the role that this mechanism plays in the pathogenesis of hypertension. Not all the aforementioned mechanisms have conclusively been shown to be age-related changes, independent of disease and lifestyle influences. In some populations, the incidence of hypertension changes little with age and the overall prevalence is low. To some extent, hypertension is an affliction of modern society. Until very recent history, humans employed the hunter–gatherer lifestyle for survival. Such 'primitive' peoples experienced vigorous daily physical activity and a diet rich in potassium and fibre and low in fat and sodium. Patterns of Nature led to periods of diminished food intake and obesity was virtually unheard of in these communities. Modern-day populations who enjoy relatively low incidences of hypertension tend to practice daily routines that more closely resemble the primitive lifestyle of old, particularly with regard to nutrition and physical activity. The blood pressure profiles of immigrants from such regions, however, may change over the course of a few generations to resemble that of the host community. The overabundance of foods rich in sodium, calories and fat in westernized societies, coupled with sedentary levels of activity, without doubt contributes to the epidemic of obesity and hypertension. With the abundance of effective medications available for the treatment of hypertension, these potentially modifiable risk factors receive far less attention than they deserve. Finally, there is a clear genetic role in the development of hypertension in some families. Such individuals are likely to develop hypertension early in life. The genetic contribution is complex, involves multiple interacting genes and is not fully understood at this time. Genetic factors are perhaps the strongest non-modifiable risk factor for hypertension.

Related clinical entities

Isolated systolic hypertension (ISH)

SBP rises gradually throughout adult life, whereas DBP peaks and plateaus in late middle-age, declining slightly thereafter. Therefore, the proportion of hypertensive patients with ISH increases with age, from 65% of patients with hypertension older than 60 years of age and over 90% in patients older than 70 years of age. The prevalence of ISH is higher in women than in men, whereas the proportion of hypertension attributable to ISH in older adults is similar across racial and ethnic groups. Of note, in decades past, the apparently inexorable rise in SBP with increasing age fostered the view that this was an adaptive response essential to support organ perfusion and an empirical formula '100 + age' was often used to estimate the 'appropriate' SBP. However, data from the FHS and other epidemiological investigations provide compelling evidence that SBP is a strong independent risk factor for incident CV events in all decades of life.[13] Hence the above formula should be discarded. ISH actually represents the outcome of hyaline change and increased arteriolar tone in the microvasculature with increased collagen deposition, loss of elastin and changes in endothelial function. Changes in endothelial function are driven by classical CV risk factors and some advocate its measurement as a surrogate for atherosclerotic disease burden. ISH also closely corresponds to increased wave reflection and studies of pulse wave parameters including differences between central and peripheral blood pressure may have prognostic and therapeutic consequences.[14]

Pulse pressure

After age 70 years, diastolic hypertension accounts for less than 10% of all patients with hypertension. In addition, the relationship between DBP and CV risk is bimodal in older individuals, with DBPs of greater than 90 mmHg associated with similar increased risk as that associated with DBPs lower than about 70 mmHg.[15] As a result, at any given level of SBP, CAD risk increases as DBP decreases.[16,17] An important implication of this observation is that pulse pressure (i.e. difference between SBP and DBP), which increases with age and is a measure of the degree of age-related vascular stiffness, emerges as a potent risk factor for CAD events in older individuals. Pulse pressure has been identified as a stronger risk factor than SBP, DBP or mean pressure in older adults in some studies.[16,17] In the FHS, with increasing age, there was a gradual shift from DBP to SBP and then to PP as the strongest predictor of CAD risk. In patients younger than 50 years of age, DBP was the strongest predictor. Age 50–59 years was a transition period when all three BP indexes were comparable predictors, and from 60 to 79 years of age, DBP was negatively related to CAD risk so that PP became superior to SBP.[18] However, a falling DBP in the elderly correlating to an increase in PP is a bad prognostic sign.

Special populations

From the standpoint of epidemiology, pathophysiology and treatment, there are important subgroups with distinctive characteristics, including elderly women, blacks, Hispanics and Asians, that require additional focus. Hypertension prevalence is less in women than in men until 45 years of age, is similar in both genders from 45 to 64 years of age and is much higher in women than men older the 65 years of age.[19] Age-adjusted hypertension prevalence, both diagnosed and undiagnosed, from 1999 to 2002 was 78% for older women and only 64% for older men.[20]

Secondary hypertension

Although most hypertension (80–90%) is essential, that is, its pathophysiological cause is unknown, secondary causes of hypertension are being increasingly recognized as contributing to morbidity. Renal artery stenosis (RAS) is more common than is usually thought and is often associated with PAD, especially if associated with a reduction in estimated glomerular filtration rate (eGFR), signs of (micro)albuminuria. Although not contributing directly to hypertension as is the case in severe stenotic disease (>85%), it is a risk factor for angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin-II receptor blocker (ARB)-induced nephrotoxicity. Any patient with these risk factors should have renal function assessed two weeks after starting an ACE-I/ARB or clinicians should be wary of slow progressive decreases in eGFR as a manifestation of RAS. Most endocrine causes of hypertension are rare (phaeochromocytoma, Cushing's disease or Conn's syndrome) but adrenal mineralocorticoid hyperplasia is common.[21] This manifests as aldosteronaemia allied with low renin and its prevalence varies in surveys from 5 to 10% of patients with hypertension. An increased prevalence of low-renin hypertension is found in the elderly, patients with diabetes and West African-derived populations. Most is not caused by adenomas but by generalized adrenal hypertrophy and can be diagnosed by finding a moderately raised aldosterone:renin ratio in a random sample taken in patients not receiving beta-blockade It often responds well to treatment with an aldosterone antagonist.

Resistant hypertension

Most hypertension is treated with polypharmacy as each individual agent reduces blood pressure by about 10%. Resistant hypertension is formally defined as a BP >140/90 mmHg after treatment with three

antihypertensive drugs.[5] Most commonly it is caused by poor compliance with polypharmacy, but other causes include ISH and contributory comorbidities including secondary hypertension and neurological hypertension. This can include anxiety states (see white coat hypertension in the section Clinical assessment and diagnosis, below), but also includes dysregulation of central mechanisms of BP regulation. The commonest cause of central dysregulation is sleep apnoea syndrome, which is often associated with obesity and can be diagnosed by oximetry studies and treated with continuous positive airways pressure maintenance (CPAP) allied commonly with weight loss.[22]

The effect of treating hypertension in the elderly – an overview of clinical trials

Salient features of the pivotal clinical trials discussed below and a summary of their findings are given in Tables 40.1 and 40.2.

The benefit of treating hypertension in the elderly was evident as early as 1967. The Veterans Administration Cooperative study, which was published in three parts between 1967 and 1972, documented the benefit of treating severe[23] and mild[24] diastolic hypertension. In subjects over the age of 60 years, a 70% reduction in the incidence of stroke and 52% reduction in cardiovascular events were observed in the treatment group.[25] Similar favourable outcomes were documented in the Australian Therapeutic Trial in Hypertension, where a 33% reduction in stroke and 18% reduction in CAD were noted in the treated subgroup age 60–69 years, compared with the placebo group.[26] In the Hypertension Detection and Follow-up Program, there was a 17% reduction in all-cause mortality after a 5 year follow-up period of patients aged 60–69 years, treated for mild diastolic hypertension.[27] These and other early studies, however, primarily treated diastolic hypertension and had relatively few participants in the geriatric age group. The subgroup 60–75 years of age in the Veterans Administration Cooperative Study represented only 20% of total enrolment. Treatment of hypertension in the elderly remained tentative and debatable until the mid-1980s, when multiple randomized trials gave credence to the benefits and safety of aggressive BP management even in advanced age. The SHEP trial addressed ISH in subjects ≥60 years of age.[28] The treatment group received chlorthalidone, with the addition of atenolol if needed, to achieve the target BP. The impact of treatment was greatest in reducing the incident of stroke by 36% and CV events by 32%. The reduction in coronary events was 27%, but not statistically significant. Comparable results were noted in the Systolic Hypertension in Europe (Syst-Eur) trial, which also studied subjects aged 60 years or older with primarily ISH.[29] Treatment was initiated with nitrendipine, with the addition of enalapril and hydrochlorothiazide if necessary. Reductions in stroke by 42%, CV events by 31% and coronary events by 26% were noted in the treatment group compared with placebo, all of which were significant. In both studies, the reductions in CV mortality (SHEP 20%, Syst-Eur 27%) and total mortality (SHEP 13%, Syst-Eur 14%) were similar and non-significant. The Systolic Hypertension in China (Syst-China) trial[30] paralleled the Syst-Eur trial and had similar enrolment criteria, but used captopril as a second-line intervention. Treatment outcome results were in line with the previous two studies, with the exception of larger and statistically significant decreases in total and CV mortality (39% in both cases), possibly due to the slightly younger age of the participants. Similarities in trial design and enrolment criteria of these three studies lend themselves to pooling analysis. When combined, reductions in strokes

Table 40.1 Characteristics of treatment trials that predominantly involved older hypertensive individuals. Trial acronyms and references are found in the body of the text.

Trial	*n*[a]	Mean age (years)	Mean baseline BP[a](mmHg)	Mean follow-up period	Treatment BP(mmHg)	Control BP(mmHg)	Mean BP difference (mmHg)	Intervention	
								First line	Second line
SHEP	4736	71.6	170/77	4.5 years	144/68	155/71	−11/−3	Chlorthalidone	Atenolol
Syst-Eur	4695	70.2	174/85	2.0 years	151/78	161/83	−10/−5	Nitrendipine	Enalapril
Syst-China	2394	66.5	171/86	3.0 years	151/81	159/84	−9/−3	Nitrendipine	Captopril
EWPHE	840	72.0	182/101	4.6 years	148/85	167/90	−19/−5	Maxzide	Methyldopa
STOP-Hyper	1627	76.0	195/102	25 months	167/87	186/96	−19/−8	Diuretic or β-blocker	Diuretic or β-blocker
MRC	4396	70.0	185/91	5.8 years	152/76	168/85	−16/−9	Diuretic or β-blocker	Diuretic or β-blocker
Coope	884	68.7	196/99	4.4 years	162/78	180/89	−18/−11	Atenolol	Diuretic
STONE	1632	66.0	168/100	30 months	146/87	156/90	−9/−5	Nifedipine	Captopril
HYVET	3845	83.6	173/90	1.8 years[b]	29.5/12.9	−14.5/6.8	−15/6.1	Diuretic	ACE inhibitor

[a] *n*, patient number; BP, blood pressure.
[b] Median follow-up.

Table 40.2 Outcome of treatment trials. Trial acronyms and references are found in the body of the text.

Trial		Stroke events (total) (%)	Cardiovascular (total) (%)	Coronary events (total) (%)	Stroke mortality (%)	Cardiovascular mortality (%)	Total mortality (%)
SHEP		−36[a]	−32[a]	−27	−29	−20	−13
Syst-Eur		−42[a]	−31[a]	−26[a]	−27	−27	−14
Syst-China		−38[a]	−37[a]	−37	−58[a]	−39[a]	−39[a]
EWPHE		−32	−38[a]	−47[a]	−32	−27[a]	−9
STOP-Hyper		−45[a]	−40[a]	−13	−76[a]	–	−43[a]
MRC		−25[a]	−17[a]	−19	−12	−9	−3
Coope		−42[a]	–	+3	−70[a]	−22	−3
STONE		−57[a]	−60[a]	−6	–	−26	−45[a]
HYVET	Diuretic	−30	−34	−28	−39	−23	−21
	ACE Inhibitor						

[a] Statistically significant ($p < 0.05$).

(37%), coronary vascular disease (25%), CV events (32%), CV mortality (25%) and total mortality (17%) were noted in the treatment group compared with placebo, all of which were statistically significant.[31]

Other studies addressed systolic–diastolic hypertension. The Swedish Trial in Older Patients with Hypertension (STOP-Hypertension) compared beta-blockers and thiazide diuretics with placebo, in patients 70–84 years of age (average 76 years) with a mean BP of 195/102 mmHg.[32] In the treatment group, significant reductions in the incidence of stroke (45%), CV events (40%) and total mortality (43%) were documented after an average 25 month follow-up period. Myocardial infarctions were reduced by only 12%, which was not statistically significant. These findings were somewhat at odds with those of the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial. The baseline SBP and DBP in the EWPHE trial ranged between 160–239 and 90–119 mmHg, respectively (average 182/101 mmHg) and treatment was with hydrochlorothiazide–triamterene for an average follow-up period of 4.6 years.[33] Unlike the STOP-Hypertension trial, the 9% decrease in total mortality and 32% decrease in stroke were not statistically significant, whereas the 47% decline in myocardial infarctions was. The significant 38% decrease in CV events was similar to that found in the STOP-Hypertension trial (40%). The Medical Research Council (MRC) Working Party trial studied both systolic and diastolic hypertension and randomized participants aged 65–74 years to a diuretic or beta-blocker treatment group or to placebo.[34] After an average follow-up period of 5.8 years, the mean BPs in the two treatment groups were similar and significantly lower than in the placebo group. The combined treatment group had a statistically significant 25% reduction in stroke and 17% reduction in CV events. The 19% reduction in coronary events, 9% reduction in CV mortality and 3% reduction in total mortality were not significant. However, when treatment groups were analysed separately, stroke and cardiac events were significantly lower in the diuretic group by 31 and 44%, respectively. The beta-blocker treatment group showed no such reduction in these endpoints. It is not surprising that outcome is related not only to risk stratification but also to the choice of antihypertensive agent. From the above trials, however, it appears that treatment of hypertension in the elderly generally has a greater impact on stroke reduction than coronary and CV event reduction and that this effect is independent of drug choice. This pattern is seen in other trials. Both the Shanghai Trial of Nifedipine in the Elderly (STONE)[35] and the Coope and Warrender Trial[35] showed a statistically significant reduction in stroke (57 and 42%, respectively) and a non-significant reduction in coronary heart disease (CHD) (6 and 3%, respectively). Neither demonstrated a sizable change in CV mortality, but the STONE trial revealed a significant 45% decrease in total mortality compared with a non-significant 3% in the Coope and Warrender trial. Variability in treatment outcome among studies is partly due to study design, but the importance of selection criteria in treatment risk/benefit determination, independent of other study parameters, must also be stressed. Subjects with higher initial SBP and wider PP are likely to experience greater treatment benefit, as are those in a higher risk stratum. It is estimated that the reduction in all-cause mortality in the highest risk group is nine times that in the lowest risk group,[37] emphasizing the importance of establishing an individualized treatment plan based on risk stratification, rather than on generalized guidelines *per se*. The above reasoning also introduces the concept of treatment risk, a principle that until recently has largely been overlooked and will be discussed shortly.

Other endpoints have been investigated in more recent studies, notably the relationship between hypertension and cognitive decline or dementia. Data from the dementia project of the Syst-Eur trial show a significantly lower rate of development of dementia in the treatment group,[38] but

the analysis was underpowered and the conclusion difficult to generalize with authority. The Study on Cognition and Prognosis in the Elderly (SCOPE) showed a non-significant 11% reduction in the incidence of cognitive decline in the group treated with candesartan compared with placebo.[39] The investigators concluded that at the very least, there is no evidence supporting a *negative* effect of treating hypertension on cognition in the elderly. The first credible evidence supporting the potential benefit of treating hypertension on dementia came from the Protection Against Recurrent Stroke Study (PROGRESS), whose primary outcome was assessing risk for recurrent stroke.[40] During a 4 year follow-up period, a 12% overall reduction in the risk of dementia was observed with treatment. This finding was not statistically significant. However, when analysed separately, the subgroup with prior stroke at baseline showed a 34% ($p = 0.3$) reduction in dementia risk, whereas the subgroup without prior stroke showed only a 1% change.

For cognitive impairment, a similar pattern was noted, with slightly more favourable results. Severe cognitive decline was defined as a drop of three or more points on the Mini Mental Status Examination (MMSE). The overall risk reduction with treatment was 19% ($p = 0.01$). In the subgroup with prior stroke at baseline, the reduction in the risk of developing severe cognitive decline was 45% ($p > 0.001$), but only 9% (not significant) in the subgroup without prior stroke.

Various meta-analysis reviews have been designed for the purpose of accommodating variability among individual trials or examining smaller subgroups within larger trials. A meta-analysis of nine trials[41] confirmed treatment benefit in the elderly. Reductions in stroke morbidity [odds ratio (RR) = 0.65; 95% CI, 0.55–0.76)], cardiac morbidity (RR = 0.85; 95% CI, 0.73–0.99) and total mortality (RR = 0.88; 95% CI, 0.80–0.97) were noted. Stroke and cardiac mortality individually were also significantly reduced in the treatment group. Another meta-analysis of eight ISH trials included 15 693 subjects.[42] There was a 30% reduction in combined fatal and non-fatal stroke events ($p > 0.0001$), a 26% reduction in combined CV events ($p > 0.0001$) and a 13% reduction in total mortality ($p = 0.02$). In untreated patients, after correcting for regression dilution bias and DBP, the relative hazard rates associated with a 10 mmHg higher baseline SBP were 1.26 ($p = 0.0001$) for total mortality, 1.22 ($p = 0.02$) for stroke, but only 1.07 ($p = 0.37$) for coronary events. Treatment benefit was greatest in men, patients with previous CV complications and those who had larger PPs. DBP was inversely correlated with total mortality, independently of SBP. Treatment effect was also largest in subjects over the age of 70 years, a topic of contention, which will be discussed next.

Despite compelling evidence supporting the benefit of treating hypertension in older persons,[43] the evidence for very old subjects is much less clear.[44–47] 'Very old' is arbitrarily defined as >80 years of age, since at that age the risk/benefit advantage begins to waver. Subjects over the age of 80 years are absent or under-represented in most clinical trials, even though this segment of the population is the fastest growing in the westernized world. The very old also tend to be lumped in the 65-and-over age group, whereas they clearly have diverse and distinct characteristics and data obtained in younger adults cannot instinctively be extrapolated to the very old. As early as 1986, trend analysis of EWPHE data suggested that treatment of hypertension is less effective, or even harmful, above the age of 80 years.[48] Other studies have shown mixed results. The SHEP trial found treatment benefit, particularly in stroke prevention, extending beyond the age of 80 years. In the Syst-Eur analysis, total and CV mortality were significantly lower for the treatment group under the age of 80 years, but not for those aged 80 years or older. The overall RR for CV events in the treatment group from the STOP-Hypertension trial was 0.60, but the benefit decreased with increasing age subgroups and crossed the unity point between the ages of 80 and 85 years. These trials enrolled relatively few very old subjects. A meta-analysis of randomized controlled studies that enrolled subjects older than 80 years of age included 1670 subjects followed for a mean period of 3.5 years.[49] A significant reduction in stroke (34%), CV events (22%) and heart failure (39%) occurred in the treatment group compared with the control group. No benefit in CV death and a non-significant 6% *increase* in all-cause deaths were observed in the treatment group. The trend became stronger when the analysis was limited to five double-blind trials – an 11% ($p = 0.41$) increase in CV mortality in the treatment group and a 14% ($p = 0.05$) increase in total mortality were observed.

Several population-based observational studies have demonstrated an inverse relationship between BP and mortality in the very old. One study[50] enrolled 83% of the population of Temper, Finland, aged 85 years or older ($n = 561$), and a similar study[51] enrolled 94% of the residents of Leiden, The Netherlands, aged 85 years or older ($n = 833$). In both studies, the chance of being alive after 5 years was greatest in those with the highest BP at enrolment. In the Temper study, subjects with SBP ≥200 mmHg at entry had a threefold higher survival rate than those whose SBP was 120–140 mmHg. Similar results were reported in the Helsinki Ageing Study,[52] where it was estimated that the 5 year mortality declined by 10% for every 10 mmHg increase in SBP at enrolment. These and earlier observational studies are limited to correlations and constrained by confounding variables in selection criteria. In the Leiden study, for example, low BP was associated with poor health. After adjusting for health status, the inverse relationship disappeared.

The HYVET study[53]

In the majority of studies to date, benefits in stroke reduction appear related to BP reduction, as a 10 mmHg reduction in SBP was associated with a 20–30% lower risk of stroke in individuals over 70 years of age. Furthermore, there is greater benefit with a greater reduction in BP. It is unclear whether the benefits are related solely to BP reduction or whether there are additional benefits conferred by class of BP medication. Although there was consistent benefit in stroke reduction when drugs were compared with placebo, there was little difference between drug classes.[54] The Hypertension in the Very Elderly Trial (HYVET) was the first interventional controlled trial designed to assess the risk and benefit of treating hypertension specifically in subjects older than 80 years of age.[53] Patients in the aforementioned studies consisted predominantly of the 'early elderly'. In HYVET, patients in the 'late elderly' group (>80 years of age with elevated SBP) were randomized to indapamide, with addition of perindopril if needed or placebo and followed over 2 years. This study showed major benefit in CVD events and a large reduction in new cardiac failure in those older than 80 years of age when treated with an ACE-I–indapamide combination to a target BP of 150/80 mmHg.[53] Patients in the indapamide arm had a 30% risk reduction in fatal or non-fatal stroke ($p = 0.06$). Although there have been consistent benefits in reduction of stroke with antihypertensive therapy in elderly patients, some reports have suggested that these benefits may be offset by an increase in death in treated patients).[49] The HYVET, however, found benefits consistent with a 21% risk reduction (95% CI, 4–35%; $p = 0.02$) of all-cause death in the indapamide arm.[53]

Evidence after HYVET[2]

The results of HYVET[53] modify previous recommendations for patients >80 years of age. In HYVET, 3845 patients >80 years of age with SBP >160 mmHg were randomly assigned to placebo or drug therapy. The latter included a non-thiazide sulfonamide diuretic (indapamide) supplemented by an ACE-I (perindopril) when needed for a target SBP of 150 mmHg. After 2 years, with about one-quarter of the patients using monotherapy and three-quarters combination therapy, the trial was stopped because drug treatment, although decreasing BP compared with the placebo group (144/78 versus 161/84 mmHg), reduced adverse outcomes. This consisted of reductions in the incidence of stroke (~30%), congestive heart failure (~64%) and CV morbid and fatal events (~23%). Most impressively, there was a significant reduction (~21%) in the incidence of all-cause death. Of importance, drug treatment was well tolerated. The reduction in BP in the standing position was similar to that in the sitting position. Furthermore, serum electrolyte and biochemical values were similar in drug- and placebo-treated groups. In fact, fewer serious adverse events were reported in the drug-treated than in placebo-treated patients.

The HYVET results provide clear evidence that BP lowering by drugs is associated with definite CV benefits in patients >80 years of age. They not only refute concern that this may lead to an increase, rather than a decrease, in mortality, but also show that in this stratum of the population, there is a prolongation of life. This finding is highly relevant for public health because subjects >80 years of age represent the fastest growing fraction of the population; the prediction is that by 2050, they will account for more than one-fifth of all elderly individuals.

However, HYVET has some limitations that should be taken into account when considering antihypertensive treatment in very elderly patients. Patients with stage 1 hypertension were not included. The patients on whom HYVET results are based are not representative of the general very elderly population. First, to limit dropouts, recruitment focused on patients in relatively good physical and mental condition and with a low rate of previous CVD. This is at variance from the high rate of frail and medically compromised patients typical in this very old age range. Second, because identifying appropriate subjects was difficult, recruitment required about six years and was only possible through participation of Eastern European countries and China, which together accounted for 98% of the patients. Furthermore, premature interruption of the trial (because of mortality benefit) made the average follow-up relatively short (median 1.8 years). It remains unknown whether benefits of antihypertensive treatment persist or diminish after two or three years. Also, the mean age was 83 years and only a small fraction was >85 years of age, which leaves open the question of whether the benefit extends to ages much older than those investigated in previous trials. Compared with placebo, drug treatment was not accompanied by significant improvement in the incidence of dementia or cognitive dysfunction. The HYVET-COG, a HYVET substudy, found a non-significant 14% decrease in dementia with active treatment versus placebo.[55] Although no specific class of antihypertensive drugs has been definitively linked with cognitive decline in the elderly, inadequate BP reduction is associated with cognitive decline. Although benefits in HYVET-COG were limited to CV outcomes, hypertension treatment was not associated with negative effects on cognition. Although there is clear evidence of the benefits of hypertension treatment in the reduction of both ischaemic and haemorrhagic stroke, the benefits in reducing cognitive impairment and dementia have only been demonstrated in the early elderly. In the patients, mean age 64 years, in PROGRESS, a perindopril-based BP-lowering regimen among patients with previous ischaemic stroke or transient ischaemic attack significantly reduced stroke-related dementia (34%) and severe cognitive decline

(19%).[56] Finally, the optimal BP goal for reducing CV events and mortality was not investigated.

Clinical assessment and diagnosis[2]

Diagnosis of hypertension should be based on at least three different BP measurements, taken on two or more separate office visits. At least two measurements should be obtained once the patient has been seated comfortably for at least five minutes with the back supported, feet on the floor, arm supported in the horizontal position and the BP cuff at heart level. With the switch from mercury to aneroid sphygmomanometers, adjustment is required to cut-offs and many societies now validate individual instruments to ensure accurate reporting.[57] All societies recommended measurement on at least three occasions as biological variation in BP is extensive and stress or exercise effects can be substantial.

Pseudohypertension is a falsely increased SBP that results from markedly sclerotic arteries that do not collapse during cuff inflation (e.g. 'non-compressible'). Although this occurs more commonly in the elderly, the actual prevalence is unclear. Identification of pseudohypertension is necessary to avoid overtreating high BP and should be suspected in elders with refractory hypertension, no organ damage and/or symptoms of overmedication and in patients with chronic renal disease with secondary hyperparathyroidism with marked arterial classification as defined by much raised ankle-brachial BP or extreme pulse wave velocities.

White coat hypertension is more common in the elderly and frequent among centenarians. The white coat effect is directly related to the seniority of the measurer, with greater effects shown for consultants (SBP +6 mmHg) than primary care practitioners (+4 mmHg) or nurses (reference group).

Ambulatory BP monitoring is recommended to confirm a diagnosis of white coat hypertension in patients with persistent office hypertension but no organ damage. Ambulatory BP monitoring (ABPM) is indicated when hypertension diagnosis or response to therapy is unclear from office visits, when syncope or hypotensive disorders are suspected and for evaluation of vertigo and dizziness and as the primary diagnostic assessment in the UK.[4] The optimum ABPM technique uses both day and night values,[58] but a 12 h day BP may be sufficient for diagnostic purposes. The equivalence points for ambulatory compared with brachial measurements are more controversial, ranging from 5/5 mmHg correction[4] to 10/5 mmHg (ISH[5]) or 12/6 mmHg depending on the studies. Some patients cannot tolerate the BP cuff used in ABPM nor have significant white coat effects in any clinical setting, and in these subjects home BP measurement can be useful even using wrist BP monitors, which are less accurate than brachial measures.

The case for using out-of-office BP readings in the elderly, particularly home BP measurements, is strong owing to potential hazards of excessive BP reduction in older people and better prognostic accuracy versus office BP. It is recommended that 12–14 measurements of BP are gathered at different times over 5–7 days to determine average home blood pressure.[59]

All patients should undergo a CVD risk assessment, including ascertainment of a family history of hypertension, diabetes or CVD, smoking status and history, measurement of weight and ideally waist circumference and measurement of lipids (total cholesterol; HDL-cholesterol), glucose (or HbA1c) and creatinine for determination of an estimated GFR using the Modified Diet in Renal Disease (MDRD) equation. If eGFR is significantly reduced ($<45\,ml\,min^{-1}$ per $1.73\,m^2$) in a hypertensive patient then a formal measurement should be made of urine albumin concentration to allow subclassification of the degree of renal impairment present. CVD risk should be calculated in all cases and total appropriate risk factor treatment instituted if the CVD risk exceeds 20%[4] or if the CHD risk exceeds 20% for the next decade.[3] In some groups, it may be appropriate to calculate lifetime CHD/CVD risk.

Management

Differences exist between guidelines about the optimal therapeutic strategies for hypertension. All antihypertensive drugs deliver ~5–10% reduction of initial BP. The only comparative trial of different major drug classes, the ALLHAT study, showed equivalence of a thiazide diuretic (chlorthalidone), an ACE-I and a calcium-channel blocker (CCB). Alpha-blockade was not recommended given its worse prognostic outcome.[60] Meta-analyses of BP trials have suggested that all classes are equivalent provided that BP reduction is achieved.[7] Guidelines have diverged in their recommendations, with an emphasis on diuretics and beta-blockers by some (JNC−7[5]), and an age-differentiated strategy recommending the use of CCBs and diuretics in the elderly. This has recently been revised following the results of the CAFE sub-study of ASCOT[61] and the results of the ACCOMPLISH study.[62] CAFE showed that, as previously suspected, beta-blockers were less effective at reducing central BP and thus stroke than other agents, and these drugs have been demoted to second-line status.[4] In ACCOMPLISH, an ACE-I–CCB combination was compared with an ACE-I–thiazide combination therapy, with superior results for the ACE-I–CCB on CVD events. Hence ACE-I and CCBs are the preferred initial antihypertensive drugs. Controversy exists about thiazide diuretics as they may not be therapeutically equivalent. Recent guidelines have suggested that chlorthalidone (not bendroflumethiazide or hydrochlorothiazide) should be the preferred thiazide and that an independent evidence base exists for indapamide (a non-thiazide diuretic).[4] There is no benefit to combining

ACE-Is with ARBs and this combination causes excess hypotension.[63]

Evidence for individual SBP targets remains poor and is derived from meta-analyses and indirectly from the DBPs achieved in the HOT study. Evidence suggests that populations at higher CVD risk should be targeted to lower BP levels, but clinicians need to remain mindful that that BP targets are based primarily on observational data in middle-aged patients and optimal targets for elderly patients, especially those with systolic hypertension and normal or low DBP (e.g. ISH), remain to be defined from randomized trial data.

The mantra of 'lower is better' suggested by the epidemiology of BP has been investigated in some high-risk groups. Both the ADVANCE and ACCORD BP trials found that among patients with type 2 diabetes mellitus at high risk for CV events, targeting SBP below 120 mmHg, as compared with below 140 mmHg, did not reduce the rate of fatal and non-fatal major CVD events and resulted in an increase in adverse experiences attributed to BP medications.[64,65]

Because hypertension increases with ageing and is also associated with longevity, there is often uncertainty about its management in very elderly patients. Until very recently, this was a particular dilemma for the very elderly because most hypertension management trials had upper age thresholds for enrolment (<70 years) and/or did not present age-specific results. However, the HYVET showed major benefit in CVD events and a large reduction in new cardiac failure in those older than 80 years of age when treated with an ACE-I–indapamide combination to a target BP of 150/80 mmHg.[53] No difference was found in outcomes between those with generalized hypertension and ISH, despite a greater therapeutic efficacy of the combination in ISH.[66]

Conclusion

Hypertension in the elderly is a major and increasing problem that should be assessed in parallel with other comorbidities and should be managed in the context of total CVD risk with no special allowance being made for chronological age.

Key points

- The prevalence of hypertension and wide PP increases with age.
- Treatment of high BP can significantly reduce the risk of CV mortality and morbidity in older persons, and the evidence for this is now also available for treating the very old.
- On the basis of current interventional trials, significant cardiovascular benefit may result from relatively small improvements in BP and the optimal SBP in the elderly may be 140–160 mmHg.
- The results from HYVET provide clear evidence that BP lowering by drugs is associated with definite CV benefits in patients >80 years of age.
- The benefits of treatment of hypertension need to be weighed against the hypotensive conditions commonly seen in the elderly, such as postprandial hypotension and postural hypotension, which can lead to syncope and falls.

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CHAPTER 41

Heart failure

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Introduction

The combination of age-related changes in the cardiovascular system and the increasing prevalence of cardiovascular disease at older age predispose the older individual to the development of heart failure (HF). As a result, HF is predominantly a disorder of older adults, with persons over age 75 accounting for more than 50% of the over 1 million hospitalizations for HF each year in the United States, and over 60% of all HF-related deaths.[1] In addition, both the incidence and prevalence of HF are increasing, primarily due to the ageing of the population, and it is anticipated that the number of older adults with clinical HF will double over the next 25 years.

In addition to its effects on hospitalizations and mortality, HF is an important cause of chronic disability in older adults, and the functional limitations imposed by HF are often a key factor contributing to entry into a long-term care facility. HF is also one of the most common comorbid conditions in hospitalized older adults who develop delirium, and HF interacts detrimentally with every major geriatric syndrome. Thus, the societal burden attributable to HF in the ageing population is extremely high, as a consequence of which HF is one of the most costly medical illnesses in the United States today, with estimated annual expenditures in excess of $39 billion, representing approximately 5% of the total healthcare budget.[1]

Pathophysiology

Cardiovascular ageing

As discussed in Chapter 35, normal ageing is associated with extensive changes in cardiovascular structure and function. Taken together, these changes result in a marked reduction in cardiovascular reserve, so that older adults are less able to maintain normal cardiac output and intracardiac pressures in response to stress, whether that stress is physiologic (e.g. exercise) or pathologic (e.g. ischaemia, anaemia, infection). Figure 41.1 illustrates the striking effect of normal ageing on maximum oxygen consumption (VO_2 max) in healthy men and women carefully screened to exclude occult cardiovascular disease. Note that the decline in VO_2 max with age is not simply linear, but that it actually accelerates after age 60. Moreover, normal octogenarians often have VO_2 max levels of less than 20 ml $O_2 min^{-1} kg^{-1}$, which are similar to those typically observed in middle-aged persons with moderate HF (New York Heart Association class II). Given the normal decline in cardiovascular reserve with increasing age, it is not difficult to understand why an 85-year-old who suffers an acute myocardial infarction (MI) is substantially more prone to develop HF and cardiogenic shock than a 65-year-old who suffers an MI of equivalent size. Similarly, older patients are more likely to develop HF in response to numerous other cardiac and non-cardiac stressors, such as atrial fibrillation (AF), pneumonia, intravenous fluid administration, or any type of major surgery.

Table 41.1 summarizes the principal effects of normal ageing on cardiovascular structure and function.[2,3] Increased vascular stiffness contributes to the progressive rise in systolic blood pressure at older age, and increases impedance to left ventricular (LV) ejection (afterload). Impaired LV relaxation during early diastole (an active, energy-requiring process) and increased myocardial stiffness markedly alter the pattern of LV diastolic filling (preload) and result in a shift in the LV pressure-volume relationship upwards and to the left (Figure 41.2). These changes result in an increased reliance on atrial contraction (the 'atrial kick') to optimize LV filling, and predispose the older individual to the development of HF with preserved LV ejection fraction (HFPEF) and AF. Diminished responsiveness to β-adrenergic stimulation attenuates the heart rate response to stress and also reduces peak contractility, both of which are dependent on activation of the cardiac β_1-receptors. In addition, peripheral vasodilation is impaired due to reduced responsiveness of arteriolar β_2-receptors, further increasing afterload and limiting skeletal muscle blood

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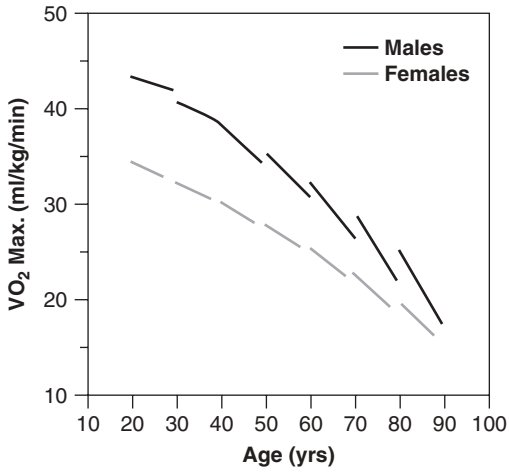

Figure 41.1 Age and VO_2max in healthy subjects: the Baltimore Longitudinal Study on Aging. Reproduced from Fleg JL *et al*. Longitudinal decline of aerobic capacity accelerates with age. *Circulation* 2000;**102**(Suppl II):II–602 [abstract], by permission of Lippincott Williams & Wilkins.

Table 41.1 Principal effects of ageing on cardiovascular structure and function.

- Increased vascular 'stiffness', impedance to left ventricular ejection, and pulse wave velocity
- Impaired left ventricular early diastolic relaxation and mid-to-late diastolic compliance
- Diminished responsiveness to neurohumoral stimuli, especially β_1 and β_2 adrenergic stimulation
- Altered myocardial energy metabolism and reduced mitochondrial ATP-production capacity
- Reduced number of sinus node pacemaker cells and impaired sinoatrial function
- Endothelial dysfunction and vasomotor dysregulation

ATP, adenosine triphosphate

flow during exercise. In healthy older adults, mitochondria in the cardiac myocytes are capable of generating sufficient ATP to meet the resting energy needs of the myocardium, but they have reduced capacity to increase ATP production in response to stress, thus further limiting peak cardiac performance. There is also a reduction in the number of functioning sinus node pacemaker cells with age, giving rise to the 'sick sinus syndrome' and contributing to chronotropic incompetence; that is, the inability to increase heart rate commensurate with demands. Finally, age-related endothelial dysfunction and vasomotor dysregulation, while not affecting cardiac performance directly, limit peak coronary blood flow and contribute to the development and progression of atherosclerosis and coronary artery disease (CAD). In summary, normal cardiovascular ageing exerts deleterious effects on all four of the major

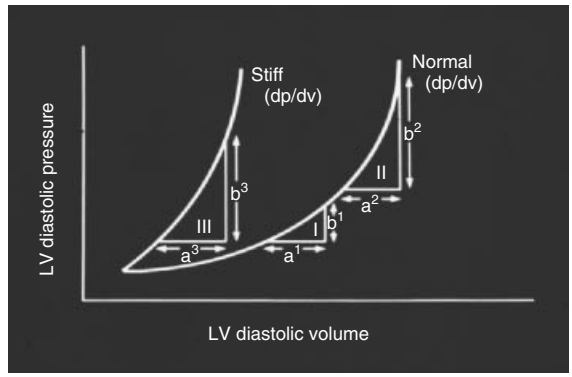

Figure 41.2 Effect of age on the left ventricular (LV) pressure-volume relationship. Note that there is a shift to the left, such that small increases in left ventricular volume are associated with greater increases in left ventricular pressure compared to younger persons. Adapted from Gaasch WH *et al*., *Am J Cardiol* 1976;**38**:645–53.

determinants of cardiac output – heart rate, contractility, preload, and afterload – thereby greatly reducing peak cardiac performance and cardiovascular reserve. In addition, cardiovascular ageing fosters the development of systolic hypertension and CAD, the two leading causes of HF in older adults.[1]

Other organ systems

Age-associated changes in other organ systems also contribute to the predilection of older adults to develop HF, and may affect the clinical features and response to therapy (Table 41.2). Renal function declines with age, and older adults are less able to excrete a salt and water load. Pulmonary reserve also declines with age, with decreased vital capacity and increased ventilation-perfusion mismatching resulting in more severe hypoxaemia in the setting of superimposed HF. The central nervous system is less able to maintain cerebral perfusion in response to decreased cardiac output due to impaired autoregulatory capacity, thus increasing the propensity of older HF patients to develop impaired cognition or overt delirium. Thirst is also impaired in older adults, increasing the risk of diuretic-induced dehydration. Sarcopenia, a hallmark of ageing, contributes to impaired exercise tolerance and diminished aerobic capacity in older HF patients. Finally, age-related alterations in the alimentary tract, liver, and kidneys result in substantial changes in the absorption, metabolism, and excretion of virtually all medications.

Clinical features

Symptoms and signs

Exertional dyspnoea, orthopnea, lower extremity swelling, and impaired exercise tolerance are the cardinal symptoms

Table 41.2 Effects of ageing on other organ systems.

Kidneys
Decline in glomerular filtration rate (GFR), ~8 cm^3 min^{-1} per decade
Impaired water and electrolyte homeostasis
Reduced plasma renin and aldosterone activity
Impaired elimination of renally excreted drugs
Lungs
Loss of elastic recoil
Increased ventilation-perfusion (V/Q) mismatching
Reduced vital capacity and minute ventilation
Nervous system
Diminished reflex responsiveness, esp. baroreceptors
Reduced central nervous system autoregulatory capacity
Impaired thirst mechanism
Musculoskeletal system
Loss of muscle mass and strength (sarcopenia)
Loss of bone mass, esp. in women (osteopenia)
Altered pharmacokinetics and pharmacodynamics of most drugs

of HF at both younger and older age. However, with increasing age, which is often accompanied by a progressively more sedentary lifestyle, exertional symptoms become less prominent. Conversely, atypical symptoms, such as confusion, somnolence, irritability, fatigue, anorexia, or diminished activity level, become increasingly more common manifestations of HF, especially after age 80.

Physical signs of HF include elevated jugular venous pressure, hepatojugular reflux, an S_3 gallop, pulmonary rales, hepatomegaly, and dependent oedema. With the exception of rales each of these features occurs less commonly in older HF patients, in part because of the increasing prevalence of HFPEF, in which signs of right HF are a late manifestation and a third heart sound is typically absent. On the other hand, behavioural changes and altered cognition, which may range from subtle abnormalities to overt delirium, frequently accompany HF at elderly age, particularly among institutionalized or hospitalized patients.

Diagnosis

Accurate diagnosis of the HF syndrome at older age is confounded in part by the increasing prevalence of atypical symptoms and signs. In addition, exertional symptoms may be attributable to non-cardiac causes, such as pulmonary disease, anaemia, depression, physical deconditioning, or ageing itself. Likewise, peripheral oedema may be due to venous insufficiency, hepatic or renal disease, or medication side effects (e.g. calcium-channel blockers), and pulmonary crepitus may be due to atelectasis or chronic lung disease. Despite these limitations, careful clinical assessment for the presence of multiple symptoms and signs should lead to the correct diagnosis in most cases.

Chest radiography is indicated when HF is suspected, and it remains the most useful diagnostic test for determining the presence of pulmonary congestion. However, chronic lung disease, altered chest geometry (e.g. due to kyphosis), or poor inspiratory effort may confound interpretation of the chest radiograph in elderly individuals.

Plasma B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) levels have been shown to be a valuable aid in distinguishing dyspnoea due to HF from that related to other causes, such as pulmonary disorders. BNP and NT-proBNP levels tend to be elevated in both systolic HF and HFPEF, and they also correlate with response to therapy and prognosis. However, levels of these peptides also increase with age in healthy individuals without HF, particularly women (Figure 41.3), and as a result, the specificity and predictive accuracy of elevated levels decline with age.[4] Nonetheless, in cases of diagnostic uncertainty, a low or normal BNP or NT-proBNP level effectively excludes acute HF, whereas markedly elevated levels provide strong evidence in support of the diagnosis.

Proper management of HF is critically dependent on establishing the pathophysiology of LV dysfunction (i.e. systolic vs. diastolic), determining the primary and any secondary aetiologies (Table 41.3), and identifying potentially treatable precipitating or contributory factors (Table 41.4). Differentiating systolic from diastolic dysfunction requires an assessment of LV ejection fraction by echocardiography, radionuclide ventriculography, magnetic resonance imaging, or contrast angiography. Among these, echocardiography is the most widely used and clinically useful non-invasive test for evaluating systolic and diastolic function. In addition, echocardiography provides important information about LV chamber size and wall thickness, atrial size, right ventricular function, the presence and

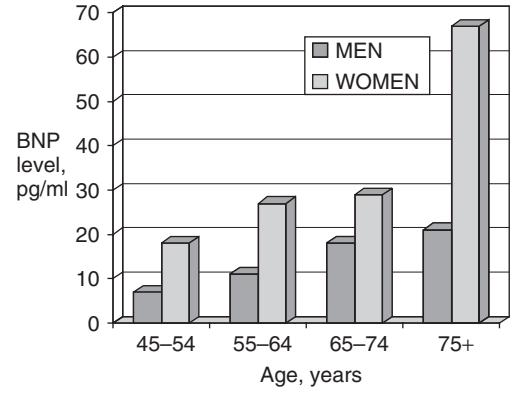

Figure 41.3 Mean B-type natriuretic peptide (BNP) levels in healthy volunteers according to age and gender. Adapted from Redfield MM *et al.*[4]

Table 41.3 Common aetiologies of heart failure in older adults.

Coronary artery disease
Acute myocardial infarction
Chronic ischaemic cardiomyopathy
Hypertensive heart disease
Hypertensive hypertrophic cardiomyopathy
Valvular heart disease
Aortic stenosis or insufficiency
Mitral stenosis or insufficiency
Prosthetic valve malfunction
Infective endocarditis
Cardiomyopathy
Dilated (non-ischaemic)
Alcohol
Chemotherapeutic agents
Inflammatory myocarditis
Idiopathic
Hypertrophic
Obstructive
Non-obstructive
Restrictive (esp. amyloid)
Pericardial disease
Constrictive pericarditis
High output syndromes
Chronic anaemia
Thiamine deficiency
Hyperthyroidism
Arteriovenous shunting
Age-related diastolic dysfunction

Table 41.4 Common precipitants of heart failure in older adults.

Myocardial ischaemia or infarction
Uncontrolled hypertension
Dietary sodium excess
Medication non-adherence
Excess fluid intake
Self-induced
Iatrogenic
Arrhythmias
Supraventricular, esp. atrial fibrillation
Ventricular
Bradycardia, esp. sick sinus syndrome
Associated medical conditions
Fever
Infections, esp. pneumonia or sepsis
Hyperthyroidism or hypothyroidism
Anaemia
Renal insufficiency
Thiamine deficiency
Pulmonary embolism
Hypoxemia due to chronic lung disease
Drugs and medications
Alcohol
Beta-adrenergic blockers (incl. ophthalmologicals)
Calcium-channel blockers
Anti-arrhythmic agents
Non-steroidal anti-inflammatory drugs
Glucocorticoids
Mineralocorticoids
Estrogen preparations
Anti-hypertensive agents (e.g. clonidine, minoxodil)

severity of valvular lesions, and pericardial disorders. For these reasons, echocardiography is recommended for all patients with newly diagnosed HF or unexplained disease progression.[5]

Other diagnostic studies that may be indicated in selected patients include an assessment of thyroid function (especially in the presence of AF), an exercise or pharmacologic stress test to evaluate for the presence and severity of ischaemia, and cardiac catheterization if revascularization or other corrective procedure (e.g. valve repair or replacement) is being contemplated.

Aetiology and precipitating factors

Systemic hypertension and CAD account for 70–80% of HF cases at older age.[1] Hypertension is the most common aetiology in older women, particularly those with preserved ejection fraction. In older men, HF is more often attributable to CAD. Other common aetiologies include valvular heart disease (especially aortic stenosis and mitral regurgitation) and non-ischaemic cardiomyopathy (Table 41.3). Importantly, HF in the elderly is frequently multifactorial, and it is thus essential to identify all potentially treatable causes.

In addition to determining aetiology, it is important to identify factors precipitating or contributing to HF exacerbations (Table 41.4). Non-adherence to medications and dietary restrictions is the most common cause of worsening HF, and patients should be closely questioned about their dietary and medication habits. Other common factors contributing to increased symptoms include ischaemia, volume overload due to excess fluid intake (self-inflicted or iatrogenic), tachyarrhythmias (especially AF or flutter), intercurrent infections, anaemia, thyroid disease, and various medications or toxins (e.g. alcohol).

Comorbidity

A hallmark of ageing is the increasing prevalence of multiple comorbid conditions, many of which impact directly or indirectly on the diagnosis, clinical course, treatment, and prognosis of HF in the elderly (Table 41.5). As noted previously, renal function declines with age, and octogenarians often have creatinine clearances of $<60\,cm^3\,min^{-1}$ (i.e. stage III chronic kidney disease), despite 'normal' serum

Table 41.5 Common comorbidities in older patients.

Condition	Implications
Renal dysfunction	Exacerbated by diuretics, ACE inhibitors, ARBs
Anaemia	Worsens symptoms and prognosis
Chronic lung disease	Contributes to uncertainty about diagnosis and volume status
Cognitive dysfunction	Interferes with dietary, medication and activity adherence
Depression, social isolation	Worsens prognosis, interferes with adherence
Postural hypotension, falls	Exacerbated by vasodilators, diuretics, beta-blockers
Arthritis	NSAIDs worsen heart failure, antagonize heart failure medications
Urinary incontinence	Aggravated by diuretics, ACE inhibitors (cough)
Sarcopenia, osteoporosis	Contribute to impaired exercise tolerance
Sensory deprivation	Interferes with adherence
Nutritional disorders	Exacerbated by dietary restrictions
Polypharmacy	Reduced adherence, increased drug interactions
Frailty	Exacerbated by hospitalization; increased fall risk

ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs

creatinine levels and in the absence of underlying renal disease. Older patients are also less able to excrete excess sodium and water, and this deficiency may contribute to volume overload. Diuretics tend to be less effective in the elderly, whereas diuretic-induced electrolyte disorders are more common, in part due to reduced capacity of the kidneys to preserve electrolyte homeostasis. Conversely, diuretics, ACE inhibitors, and angiotensin receptor blockers (ARBs) can all contribute to worsening renal function, and older patients are at increased risk for this complication.

Older HF patients are at increased risk for anaemia due to comorbid chronic illnesses (renal disease, occult malignancy), inadequate dietary intake of key nutrients (iron, folate, B_{12}), and use of medications associated with gastrointestinal blood loss (aspirin, warfarin, non-steroidal anti-inflammatory drugs). Anaemia contributes to impaired tissue oxygen deliver and impaired exercise tolerance, and may exacerbate myocardial ischaemia in patients with underlying CAD. Anaemia has also been shown to be an independent predictor of adverse clinical outcomes in patients with HF.

Normal ageing is associated with a decline in maximum voluntary ventilation and an increase in ventilation-perfusion mismatching. In addition, chronic obstructive and restrictive lung diseases further impair pulmonary function in many older adults. Diminished pulmonary function, in turn, contributes to increased dyspnoea and exercise intolerance in older patients with HF, as the lungs are unable to compensate for impaired cardiac performance. In addition, the presence of chronic lung disease often leads to diagnostic uncertainty (is the patient's dyspnoea due to HF, pulmonary disease, or a combination of both?), in part by confounding interpretation of the physical examination and chest radiograph.

Cognitive dysfunction interferes with the patient's ability to participate fully in self-care behaviours, such as weight monitoring and adherence to dietary restrictions and prescribed medications. In more severe cases, cognitive impairment substantially limits the patient's ability to provide a reliable medical history, and may prevent recognition of new or worsening symptoms. Patients with cognitive dysfunction are also at increased risk for developing delirium, which may complicate hospital management and predispose to serious adverse events (e.g. falls, aspiration, infections).

Up to 20% of elderly HF patients have clinically significant depression, which is often unrecognized. Social isolation, primarily due to the death of one's spouse, also occurs with increasing frequency at elderly age. These conditions have both been associated with adverse outcomes in elderly HF patients, including increased mortality and hospitalization rates, in part due to reduced adherence to prescribed medications and other recommended behaviours. In addition, depression has been linked with increased adrenergic tone and ventricular arrhythmias in patients with cardiovascular disease, both of which confer an increased mortality risk in HF patients.

Increased vascular stiffness and impaired baroreflex responsiveness predispose older adults to the development of postural hypotension, while age-related alterations in sinus node function increase the risk of bradyarrhythmias (sick sinus syndrome). In addition, balance and proprioception decline with age. Taken together, these factors greatly increase the risk of falls in older adults. Standard HF therapies, including diuretics, vasodilators, and beta-blockers, all have the potential to further increase the risk of falls and associated morbidity.

Arthritis is the leading cause of chronic disability in older adults, and is widely treated with non-steroidal anti-inflammatory drugs (NSAIDs) available both by prescription and over-the-counter. These agents enhance renal sodium and water reabsorption and have been associated with a significant increase in the risk of hospitalization for HF, even among patients with no prior HF history.[6] NSAIDs also antagonize the effects of diuretics and ACE inhibitors, and may inhibit the beneficial effects of aspirin in patients with CAD. In addition, NSAIDs are a

common cause of gastrointestinal bleeding in older adults, thus potentiating the risk of anaemia.

The prevalence of urinary incontinence increases with age, affecting up to 35% of women and 20% of men over the age of 80. Diuretics and ACE inhibitors (ACE inhibitor cough) may aggravate incontinence in many patients. However, most patients with mild to moderate incontinence do not report the condition to their physicians unless specifically asked. Instead, they will avoid taking their medication rather than risking embarrassment, especially if they are going to be away from home without ready access to a restroom. Although the importance of urinary incontinence as a cause of medication non-adherence in the elderly is unknown, it is likely under-appreciated, as most clinicians do not routinely inquire about this condition.

Sarcopenia contributes to muscle weakness and impaired exercise tolerance in older persons with or without HF. Osteopenia and osteoporosis compromise the structural integrity of the skeletal system (e.g. as a result of compression fractures), further reducing exercise capacity. In addition, the risk of falls and hip fractures is increased, and, as noted above, these risks may be aggravated by several of the medications used to treat HF.

Reduced visual and auditory acuity often interfere with patients' ability to comply with therapeutic recommendations, either because they did not hear the instructions properly, or because they are unable to read printed materials (e.g. medication instructions, pill bottles, nutrition labels). When coupled with social isolation, these deficits can make it particularly difficult for older patients to adhere to HF therapy.

Under-nutrition is common in older adults and is usually multifactorial, with reduced access to nutritional foods (e.g. due to loss of independence, social isolation, limited finances), diminished appetite (due to chronic illness, depression, medications), loss of enjoyment from eating (impaired sense of taste and smell, social isolation), neuromuscular conditions (stroke, Parkinsonism), and mechanical factors (poor dentition, difficulty swallowing) all playing a role. In addition, prevalent medical conditions often lead to the imposition of major dietary restrictions, including protein restriction in patients with hepatic or renal disease, carbohydrate restriction in diabetics, fat and cholesterol restriction in patients with CAD or diabetes, and sodium restriction in patients with hypertension, HF, or renal disease. Moreover, advanced HF itself is often associated with a progressive decline in lean body mass, a condition referred to as cardiac cachexia. Thus, HF *per se*, as well as its treatment (sodium restriction in almost all cases, restriction of other macronutrients in many cases due to prevalent comorbidities), may contribute to the development or progression of under-nutrition in older adults, a condition associated with immune deficiency, frailty and a poor long-term prognosis.

Polypharmacy is common in patients with HF, since drug therapy for HF alone often entails the use of three or more medications, and virtually all elderly HF patients have associated conditions for which they are receiving treatment. Apart from the high cost associated with the use of multiple medications, polypharmacy has an important role in interfering with medication adherence, since the more medications a patient is taking, the less likely it becomes that they are taking their medications correctly. In addition, there is an exponential relation between the number of medications and the risk of drug interactions, such that patients taking 10 or more medications have over a 90% probability of experiencing one or more clinically significant drug interactions.

The prevalence of frailty increases markedly with age, especially among persons over the age of 80, and the cardinal features of frailty – weight loss, weakness, slow movement, low physical activity and exhaustion – overlap significantly with the symptoms of HF.[7] Frailty confers a poor prognosis, as it tends to be associated with progressive physical and functional decline, and it is also a marker for increased risk for iatrogenic complications, such as falls related to medications. Frailty tends to worsen during hospitalization for acute illness (e.g. a HF exacerbation), and frail patients rarely return to their previous level of function following hospital discharge. Thus, HF and frailty interact in a way that is detrimental to both conditions.

Recent studies indicate that both the number and nature of non-cardiac comorbidities have a significant impact on clinical outcomes in older HF patients. In 2003, Braunstein *et al*. examined the prevalence of non-cardiac comorbidities in Medicare beneficiaries hospitalized with HF.[8] As shown in Figure 41.4, 86% of patients had two or more non-cardiac comorbidities, and more than 25% had six or more non-cardiac conditions. In addition, since common geriatric syndromes, such as dementia, depression, incontinence and frailty, are often clinically unrecognized, it is likely

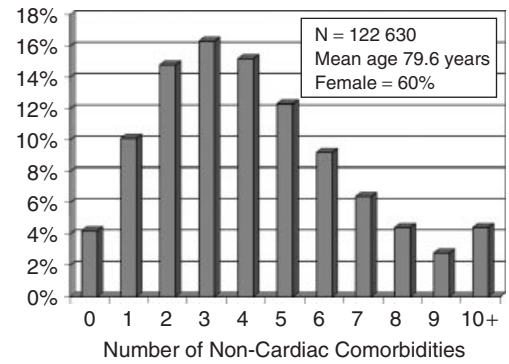

Figure 41.4 Prevalence of non-cardiac comorbidities in Medicare beneficiaries with heart failure. Adapted from Braunstein JB *et al*.[8]

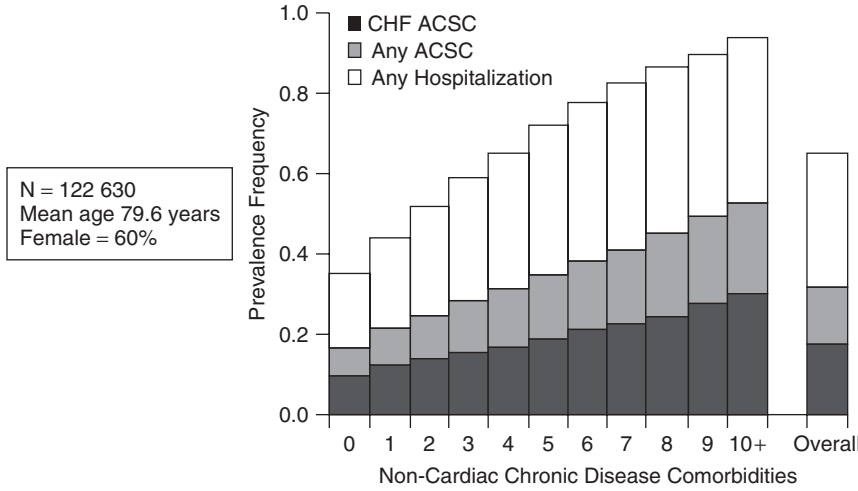

Figure 41.5 Impact of non-cardiac comorbidities on hospital admissions in Medicare beneficiaries with heart failure. ACSC, ambulatory care sensitive conditions; CHF, chronic heart failure. Reproduced from Braunstein JB *et al.*[8] Copyright 2003, with permission from Elsevier.

that the true prevalence of non-cardiac comorbidities is underestimated by Braunstein's data.

Figure 41.5 illustrates the relationship between the number of non-cardiac comorbidities and the number of hospital admissions among HF patients.[8] Overall, the proportion of patients hospitalized annually increased from about 35% among patients with no comorbidities, to over 90% among patients with nine or more comorbidities. Moreover, approximately half of all hospitalizations were considered potentially avoidable (depicted by the shaded regions in the figure), regardless of the number of comorbidities.

Several studies have examined the relationship between specific comorbidities and clinical outcomes. Chronic renal insufficiency and anaemia have both been shown to be independent predictors of mortality in elderly HF patients, and the presence of cognitive dysfunction has been associated with a striking increase in mortality among older patients hospitalized with HF. In addition, the use of NSAIDs has been associated with a 60% increase in the risk of hospitalization for HF among elderly patients with no prior history of heart disease, and a 10-fold increase among patients with pre-existing cardiac conditions.[6]

In summary, older HF patients almost invariably have one or more age-associated conditions that influence the diagnosis, clinical features, and/or management of HF. Conversely, HF and its therapy often have ramifications for the clinical course and treatment of these comorbid conditions. Consideration of the interactions between HF and prevalent comorbidities is thus a critically important aspect of management in the elderly HF patient.

Management

The principal goals of HF therapy are to relieve symptoms, maintain or enhance functional capacity and QOL, preserve independence, and reduce mortality. Although it is often stated that quality of life is more important than quantity of life in the very elderly, there is wide variability in personal preferences concerning these outcomes. Furthermore, since the elderly HF population is characterized by marked heterogeneity in terms of lifestyle, comorbidity, and personal goals and perspectives, management of HF in the elderly must first and foremost be individualized and patient-centred in accordance with each patient's circumstances and needs.

The approach to HF management involves identification and treatment of the underlying aetiology and any contributing factors, implementation of an effective therapeutic regimen, and coordination of care through the use of a multidisciplinary team.

Aetiology and precipitating factors

Although HF in older adults is rarely 'curable', proper treatment of the underlying aetiology often improves symptoms and delays disease progression. Thus, hypertension should be treated aggressively, and CAD should be managed appropriately with medications and/or percutaneous or surgical revascularization. Similarly, therapy for diabetes and dyslipidaemia should be optimized, smoking should be strongly discouraged, and a suitable level of regular physical activity should be prescribed. Alcohol intake should be limited to no more than two drinks per day in men and 1 drink per day in women, and alcohol use should be strictly proscribed in patients with suspected alcoholic cardiomyopathy.

Severe aortic stenosis is a common cause of HF at older age, and aortic valve replacement is effective in reducing mortality and improving QOL. Peri-operative mortality rates are acceptable (less than 10%), and long-term results are excellent, even in octogenarians. More recently, percutaneous aortic valve replacement has been shown to offer an effective alternative to valve replacement in selected patients with prohibitive operative risk.

Severe mitral regurgitation may be amenable to surgical therapy (i.e. valve repair or replacement) in selected patients, but the operative results are somewhat less favourable than for aortic valve surgery. Percutaneous approaches to reducing the severity of mitral regurgitation have recently been developed and offer an alternative to surgery in some cases. Mitral valve replacement is also effective therapy for severe mitral stenosis; rarely, percutaneous mitral balloon valvuloplasty may be feasible in older patients.

Atrial fibrillation is a common precipitant of HF in older patients, especially in the setting of diastolic dysfunction. In patients with recent onset symptomatic AF, many clinicians recommend restoration and maintenance of sinus rhythm if feasible, although the long-term benefits of this approach have not been established. In patients with chronic AF, the ventricular rate should be adequately controlled both at rest and during activity. Bradycardia is a less common cause of HF; when present, implantation of a permanent pacemaker provides definitive therapy (see section on Device therapy). Anaemia, thyroid disease, and other systemic illnesses should be identified and treated accordingly.

The importance of adherence to medications and dietary restrictions, including avoidance of excessive fluid intake, cannot be overemphasized. NSAIDs are widely used by older individuals to treat arthritis and relieve chronic pain, but these agents promote sodium and water retention, interfere with the actions of ACE inhibitors and other antihypertensive agents, and may worsen renal function; their use should be avoided whenever possible.[6] Similarly, the use of other medications that may aggravate HF should be closely monitored.

Pharmacotherapy

The design of an effective therapeutic regimen is based in part on whether the patient has predominantly systolic HF or predominantly HFPEF. Although these two abnormalities frequently co-exist (indeed, virtually all individuals over age 70 have some degree of diastolic dysfunction), for purposes of this discussion patients with an ejection fraction <45% (i.e. moderate or severe LV systolic dysfunction) will be considered as having systolic HF, whereas patients with an ejection fraction ≥45% will be considered as having HFPEF.

Systolic heart failure

In the past 30 years there has been considerable progress in the treatment of systolic HF. Although most studies have either excluded individuals over 75–80 years of age, or have enrolled too few elderly subjects to permit definitive conclusions, the available data indicate that the response of older patients to standard therapies is similar to that of younger patients. Therefore, current recommendations for drug treatment of systolic HF are similar in younger and older patients.[5]

ACE inhibitors

ACE inhibitors are the cornerstone of therapy for LV systolic dysfunction, whether or not clinically overt HF is present.[5] Older patients are more likely than younger patients to have potential contraindications to ACE inhibitors (e.g. renal dysfunction, renal artery stenosis, orthostatic hypotension), and they may also be at increased risk for ACE inhibitor-related side effects, such as worsening renal function, electrolyte disturbances, and hypotension. Nonetheless, a trial of ACE inhibitors is indicated in virtually all older patients with documented LV systolic dysfunction.

In most cases, ACE inhibitor therapy should be initiated at a low dose (e.g. captopril 6.25–12.5 mg tid or enalapril 2.5 mg bid), and the dosage should be gradually titrated upward to the level shown to be effective in clinical trials (captopril 50 mg tid, enalapril 10 mg bid, lisinopril 20 mg qd, ramipril 10 mg qd). Once a maintenance dose has been achieved, substituting a once-daily agent (e.g. lisinopril or ramipril) at equivalent dosage may facilitate adherence. Blood pressure, renal function, and serum potassium levels should be monitored closely during dose titration and periodically during maintenance therapy. In patients unable to tolerate standard ACE-inhibitor dosages due to side effects, dosage reduction is appropriate, as there is evidence that even very low doses of these agents (e.g. lisinopril 2.5–5 mg qd) provide some degree of benefit.

Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) have a somewhat more favourable side effect profile than ACE inhibitors, and the effects of ARBs on major clinical outcomes (mortality, hospitalizations) are similar to those seen with ACE inhibitors.[9] ARBs have also been shown to reduce mortality and hospitalizations in patients with systolic HF who are intolerant to ACE inhibitors due to cough or other side effects.[10] Compared with an ACE inhibitor alone, combining an ARB with an ACE inhibitor reduces HF admissions but not mortality, while increasing the risk of side effects.[9,11] Based on available evidence, ACE inhibitors are still considered first-line therapy for systolic HF, but ARBs offer an excellent alternative for patients intolerant to ACE inhibitors, and they may also be useful as adjunctive agents in selected patients with persistent symptoms despite conventional treatment.[5]

Hydralazine and isosorbide dinitrate

The combination of hydralazine 75 mg qid and isosorbide dinitrate 30–40 mg qid was associated with decreased mortality in a small trial of HF patients less than 75 years of age. In a more recent study that did not exclude older subjects, the combination was shown to reduce mortality in

African-American patients with symptomatic systolic HF.[12] Based on this study, combination hydralazine-nitrate therapy is recommended for self-declared African-Americans with advanced systolic HF.[5] The combination also provides an alternative therapy for patients who are intolerant to ACE inhibitors and ARBs, for patients with significant renal insufficiency, and as adjunctive therapy in patients who remain highly symptomatic despite standard treatment. Side effects are common with both hydralazine and high-dose nitrates, and the combination is not available in a once-daily formulation.

Beta-blockers

Beta-blockers improve LV function and decrease mortality in a broad population of HF patients, including those with New York Heart Association (NYHA) class IV symptoms and patients up to 80 years of age, and beta-blockers are now considered standard therapy for clinically stable patients without major contraindications.[5] Use of beta-blockers in older patients may be limited by a higher prevalence of bradyarrhythmias and severe chronic lung disease, and older patients may also be more susceptible to the development of fatigue and impaired exercise tolerance during long-term beta-blocker administration.

Carvedilol, metoprolol, and bisoprolol have all been shown to improve outcomes in patients with systolic HF, and one randomized trial found that carvedilol 25 mg twice daily was more effective than metoprolol 50 mg twice daily in reducing mortality.[13] In most cases, beta-blocker treatment should be initiated at low dosages in stable patients upon a background of ACE inhibitor and diuretic therapy. Recommended starting dosages are carvedilol 3.125 mg bid, metoprolol 6.25–12.5 mg bid, and bisoprolol 1.25 mg once daily. The dose should be gradually increased at 2–4 week intervals to achieve maintenance dosages of carvedilol 25–50 mg bid, metoprolol 50–100 mg bid (or, preferably, sustained release metoprolol 100–200 mg daily), or bisoprolol 5–10 mg daily. Lower dosages and a slower titration protocol may be appropriate in patients over 75 years of age. Contraindications to beta-blockade include marked sinus bradycardia (resting heart rate <45–50 bpm), PR interval ≥0.24 s, heart block greater than first degree, systolic blood pressure <90–100 mmHg, active bronchospastic lung disease, and severe decompensated HF.

Digoxin

Digoxin improves symptoms and reduces hospitalizations in patients with symptomatic systolic HF treated with ACE inhibitors and diuretics, but has no effect on total or cardiovascular mortality. The effects of digoxin are similar in younger and older patients, including octogenarians,[14] and digoxin is therefore a useful drug for the treatment of systolic HF in patients of all ages who have limiting symptoms despite standard therapy.

The volume of distribution and renal clearance of digoxin decline with age. In addition, the optimal therapeutic concentration for digoxin appears to be 0.5–0.9 ng ml^{-1};[15] higher concentrations are associated with increased toxicity but no greater efficacy.[15] For most older patients with preserved renal function (estimated creatinine clearance ≥60 $cm^3 min^{-1}$), digoxin 0.125 mg daily provides a therapeutic effect. Lower dosages should be used in patients with renal insufficiency. Although routine monitoring of serum digoxin levels is no longer recommended, it seems reasonable to measure the serum digoxin concentration 2–4 weeks after initiating therapy to ensure that the level does not exceed 0.9 ng ml^{-1}. In addition, a digoxin level should be obtained whenever digoxin toxicity is suspected.

Digoxin side effects include arrhythmias, heart block, gastrointestinal disturbances, and altered neurological function (e.g. visual disturbances). Although older patients are often thought to be at increased risk for digitalis toxicity, this was not confirmed in an analysis from the Digitalis Investigation Group (DIG) trial.[14] On the other hand, digoxin has significant drug interactions with many medications commonly prescribed to older patients. Among these, cholestyramine and phenytoin reduce digoxin levels, whereas amiodarone, amphotericin, calcium preparations, cyclosporine, erythromycin, itraconazole, propafenone, quinidine, reserpine, tetracycline and verapamil all increase serum digoxin concentrations and the risk of digoxin toxicity.

Diuretics

Diuretics are an essential component of therapy for most patients with HF, and diuretics remain the most effective agents for relieving congestion and maintaining euvolemia. Some patients with mild HF can be effectively controlled with a thiazide diuretic, but the majority will require a loop diuretic such as furosemide, bumetanide, or torsemide. In patients with more severe HF or significant renal dysfunction (serum creatinine ≥2.0 mg dl^{-1}), the addition of metolazone 2.5–10 mg daily may be necessary to achieve effective diuresis.

In general, diuretic dosages should be titrated to eliminate signs of pulmonary and systemic venous congestion. Common side effects include worsening renal function (often due to over-diuresis) and electrolyte disorders. To minimize these effects, renal function and serum electrolyte levels (sodium, potassium, magnesium) should be monitored closely during the initiation and titration phase of diuretic use, and periodically thereafter.

Aldosterone antagonists

Spironolactone is a potassium-sparing diuretic that acts by antagonizing aldosterone. The addition of spironolactone 12.5–50 mg daily to standard HF therapy has been shown to reduce mortality and hospital admissions

in patients with NYHA class III–IV systolic HF, with similar benefits in older and younger patients.[16] Eplerenone, a selective aldosterone antagonist, has also been shown to reduce mortality and sudden cardiac death in patients with LV systolic dysfunction following acute myocardial infarction.[17] Spironolactone is contraindicated in patients with severe renal insufficiency or hyperkalaemia, and up to 10% of patients develop painful gynaecomastia. In addition, older patients receiving spironolactone in combination with an ACE inhibitor or ARB may be at increased risk for hyperkalaemia, particularly in the presence of pre-existing renal insufficiency or diabetes, and at doses in excess of 25 mg per day. Combined use of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended.[5]

Approach to treatment

Figure 41.6 provides a suggested approach to the pharmacologic treatment of systolic HF. All patients with LV systolic dysfunction, whether asymptomatic or symptomatic, should receive an ACE inhibitor (or an ARB or alternative vasodilator if ACE inhibitors are contraindicated or not tolerated). Patients with stable symptoms and no contraindications should also receive a beta-blocker, and diuretics should be administered in sufficient doses to maintain euvolemia. Spironolactone should be used in patients with persistent NYHA class III–IV symptoms, and combination therapy with hydralazine-nitrates is indicated in black patients with symptomatic systolic HF. Digoxin and/or additional vasodilator therapy should be considered in patients who remain symptomatic despite the above regimen.

Heart failure with preserved ejection fraction (HFPEF)

Over 50% of elderly HF patients have preserved LV systolic function. However, although there have now been several clinical trials involving patients with HFPEF (Table 41.6), management of this condition remains largely empiric. As with systolic HF, the underlying cardiac disorder and associated contributing conditions should be treated appropriately. In particular, hypertension and CAD should be managed aggressively. Diuretics should be used judiciously to relieve congestion while avoiding over-diuresis and pre-renal azotemia. Topical or oral nitrates may be beneficial in reducing pulmonary congestion and orthopnea.

In the CHARM-preserved trial (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), the ARB candesartan reduced HF admissions by 16% but had no effect on mortality in patients with HF and a LV ejection fraction >40%.[18] The mean age of patients in CHARM-preserved was 67 years, and 807 patients, comprising 27% of the total population, were ≥75 years of age. However, patients with substantial comorbidity were excluded, so the applicability of the study findings to older HF patients encountered in clinical practice remains unknown.

More recently, the I-PRESERVE trial (Irbesartan in Heart Failure with Preserved Systolic Function) randomized 4128 patients (mean age 72 years, 60% women) with HFPEF (LV ejection fraction ≥45%) to the ARB irbesartan or placebo and followed them for a mean of 4.1 years.[19] In this study, irbesartan failed to show a beneficial effect on the primary composite endpoint of all-cause mortality or cardiovascular hospitalization. Irbesartan also had no effect

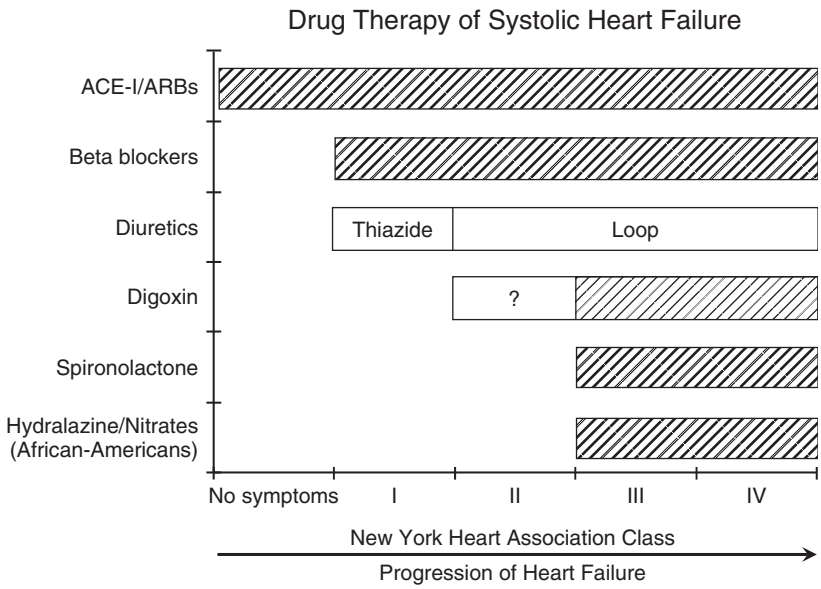

Figure 41.6 Approach to treatment of systolic heart failure; see text for details. Shaded areas refer to therapies proven to be efficacious in prospective randomized clinical trials. ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers.

Table 41.6 Treatment of heart failure with preserved ejection fraction: overview of randomized trials.

Trial	Agent	N	Mean age (years)	Follow-up (years)	Main findings
CHARM-Preserved[18]	candesartan	3023	67	3.1	No effect on mortality; HF admissions reduced
I-PRESERVE[19]	irbesartan	4128	72	4.1	No effect on mortality, admissions, or other endpoints
PEP-CHF[20]	perindopril	850	76	2.1	No effect on mortality; HF admissions reduced; improved NYHA class and exercise tolerance
SENIORS[21]	nebivolol	2128	76	1.8	No effect on mortality; decreased cardiovascular admissions
DIG-ancillary[22]	digoxin	988	67	3.1	No effect on mortality or cardiovascular admissions

HF, heart failure; NYHA, New York Heart Association

on any of the pre-specified secondary endpoints, including cardiovascular mortality and admission for HF.

In another study, PEP-CHF (Perindopril in Elderly Patients with CHF), 850 patients age 70 years or older (mean age 76 years, 55% women) with HFPEF were randomized to the ACE-inhibitor perindopril or placebo and followed for a mean of 2.1 years.[20] Although perindopril had no effect on the primary outcome of mortality or HF admission, overall HF admissions were reduced and New York Heart Association class and six-minute walk distance were improved at one year in patients randomized to perindopril. In subgroup analysis, perindopril appeared to have a beneficial effect on the primary outcome in patients ≤age 75, but not in those >75 years of age.

Although beta-blockers are of proven benefit in patients with systolic HF, there are limited data on their use in patients with HFPEF. In the SENIORS trial (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors), 2128 HF patients ≥70 years of age (mean age 76 years, 35% women) were randomized to the beta-blocker nebivolol or placebo and followed for an average of 21 months.[21] Patients with either systolic HF or HFPEF were included, and the primary composite endpoint was all-cause mortality or cardiovascular hospitalization. Overall, nebivolol was associated with a significant 15% reduction in the primary endpoint. There was no effect on mortality but cardiovascular admissions were reduced, with similar findings in patients with LV ejection fraction >35% versus ≤35%.

Finally, in the DIG ancillary trial (Digitalis Investigation Group), 988 patients (mean age 67 years, 41% women) with HF and LV ejection fraction >45% were randomized to digoxin or placebo and followed for an average of 3.1 years.[22] Overall, digoxin had no effect on the primary composite endpoint of HF death or HF hospitalization; there was also no effect on all-cause mortality, cardiovascular mortality, or cardiovascular hospitalizations.

In summary, despite publication of several prospective clinical trials in older patients with HFPEF, to date no pharmacological intervention has been shown to reduce mortality in this population, and, with the exception of diuretics to relieve congestion, there are currently no class I or class IIa indications for any of these agents in the treatment of HFPEF. Therefore, therapy should be individualized and guided by prevalent comorbidities and the observed response to specific therapeutic interventions.

Device therapy

Although most older HF patients can be effectively managed with behavioural interventions and medications, implantable devices are playing an increasingly important role in the management of selected subgroups of the HF population.

Cardiac pacemakers

Ageing is associated with a progressive decline in the number of functioning sinus node pacemaker cells, often leading to the 'sick sinus syndrome', which is characterized by inappropriate sinus bradycardia, sinus pauses, and chronotropic incompetence (failure to adequately increase heart rate in response to increased demands). Since cardiac output is directly proportional to heart rate (Cardiac Output = Heart Rate x Stroke Volume), age-related bradyarrhythmias may contribute to HF symptoms and impaired exercise tolerance. Because there is no effective medical therapy for sick sinus syndrome, implantation of a pacemaker is appropriate in symptomatic patients. Beta-blockers may precipitate symptomatic bradyarrhythmias in elderly HF patients. However, since beta-blockers improve ventricular function and reduce mortality and hospitalizations in patients with systolic HF, placement of a pacemaker is often preferable to discontinuation of beta-blocker therapy.

Cardiac resynchronization therapy (CRT)

In the past decade, a new role has emerged for pacemakers in treating selected patients with advanced HF. Approximately 30% of HF patients have left bundle branch block or other intraventricular conduction abnormality resulting in significant prolongation of the QRS interval

(≥120 ms). In these patients, LV contraction is often dyssynchronous and out of phase with right ventricular contraction. Biventricular pacing, with one lead pacing the right ventricle and a second lead pacing the left ventricle through retrograde insertion into the coronary sinus, can 'resynchronize' ventricular contraction, thus improving ejection fraction and cardiac output. The addition of atrial pacing may provide further benefit by optimizing the timing of atrial and ventricular contraction. The benefits of CRT in improving ejection fraction, reducing LV cavity size, and enhancing exercise tolerance and QOL have now been documented in several randomized trials involving patients with advanced HF symptoms (New York Heart Association class III–IV), reduced ejection fraction, and prolonged QRS duration.[23] In addition, meta-analysis indicates that CRT is associated with fewer hospitalizations and improved survival.[24] Although few older patients have been enrolled in the CRT trials, observational data suggest that CRT is associated with improved QOL and exercise tolerance in older patients, including octogenarians.[25] Based on these findings, CRT is a reasonable option for carefully selected older patients with advanced HF symptoms despite conventional therapies.

Implantable cardioverter-defibrillators (ICDs)

Approximately 40% of all deaths in patients with HF occur suddenly, and the majority of these are attributable to ventricular tachycardia (VT) and ventricular fibrillation (VF). ICDs have the capacity to recognize VT and VF, and to restore normal rhythm either by pacing techniques (in the case of VT) or by delivering an intracardiac electrical shock (refractory VT or VF). Moreover, these devices have been shown to significantly improve survival in certain high-risk subgroups of the HF population, including those with resuscitated cardiac arrest, symptomatic sustained VT, and ischaemic or non-ischaemic cardiomyopathy with ejection fraction ≤35%.[26]

In the United States, over half of ICDs are implanted in patients 65 years of age or older, including almost 20% in patients age 80 or older. However, despite the established benefits of ICDs in appropriately selected patients, the clinical role of ICDs in elderly HF patients remains a subject of debate. Data supporting the use of ICDs in patients 80 years of age or older is limited, and a recent meta-analysis found that ICDs did not reduce mortality in women.[27] ICDs also do not improve survival during the first year following implantation, so that patients with limited life expectancy (e.g. New York Heart Association class IV HF) are not suitable candidates for an ICD.[5] In addition, the devices are expensive, and QOL may be impaired, especially in patients who receive one or more ICD shocks. There are also ethical questions, such as how and when to turn off the device in the terminal stages of HF, or in cases where another life-threatening illness develops (e.g. stroke or cancer). In part for these reasons, many older patients who fulfil guideline criteria for an ICD may elect to forego the procedure. Although additional study is needed, it is clear that the use of ICDs in older HF patients must be individualized, especially for those 80 years of age or older, limited life expectancy, or impaired quality of life.

Multidisciplinary care

The presence of multiple comorbid conditions, polypharmacy, dietary concerns, and a host of psychosocial and financial issues frequently complicate the management of HF in older patients. Moreover, these factors often contribute to poor outcomes in older adults, including frequent hospitalizations. To address these issues, and to provide comprehensive yet individualized care for older HF patients, a coordinated multidisciplinary approach is recommended. Several randomized trials and meta-analyses have documented the efficacy of multidisciplinary HF disease management programmes in reducing hospitalizations and improving QOL in older patients, and these interventions have also been reported to lower overall medical costs.[28]

Elements of an effective HF disease management programme include patient and caregiver education, enhancement of self-management skills, optimization of pharmacotherapy (including consideration of polypharmacy issues), and close follow-up.[5] The structure of a HF disease management team is similar to that of a multidisciplinary geriatric assessment team, and typically includes a nurse coordinator or case manager, dietician, social worker, clinical pharmacist, home health representative, primary care physician and cardiology consultant. Specific goals of disease management are to improve patient adherence to medications, diet and exercise recommendations by enhancing education and self-management skills; provide close follow-up and improved healthcare access through telephone contacts, home health visits, and nurse or physician office visits; and optimize the medication regimen by promoting physician adherence to recommended HF treatment guidelines,[5] simplifying and consolidating the regimen when feasible, eliminating unnecessary medications, and minimizing the risks for drug–drug and drug–disease interactions.

Exercise

Both HF and normal ageing are associated with reduced exercise capacity, in part due to sarcopenia (loss of muscle mass) and alterations in skeletal muscle blood flow and metabolism. Regular physical activity improves exercise performance in healthy older adults, as well as in those with HF, and regular exercise is now recommended for most older HF patients. In the recently reported

HF-ACTION trial (HF: A Controlled Trial Investigating Outcomes of Exercise Training), 2331 patients (mean age 59 years, 28% women) with systolic HF (mean ejection fraction 25%) were randomized to a supervised exercise programme or usual care and followed for an average of 30 months.[29] Overall, there was no difference between groups in the primary composite outcome of all-cause mortality or all-cause hospitalization. After adjusting for baseline prognostic factors, exercise was associated with a significant 11% reduction in the primary endpoint and a 15% reduction in cardiovascular mortality or HF hospitalization, with similar results in patients $\leq$70 versus >70 years of age. In addition, patients randomized to the exercise group reported modest but significant improvements in QOL that persisted up to four years.[30]

Although supervised exercise programmes have been associated with the greatest improvements in exercise performance, such programmes are not feasible for many older patients due to lack of availability, travel concerns and cost constraints. Therefore, most older HF patients should be encouraged to engage in a self-monitored home exercise programme that includes stretching exercises, resistance exercises and aerobic activities. Stretching increases or maintains muscle flexibility and reduces the risk of injury. A daily stretching routine lasting 15–30 minutes and involving all major muscle groups is recommended. Resistance training increases muscle mass and strength and reduces the risk of falls and frailty. Older adults initiating a strength training programme should use light weights and perform 2 to 3 sets of 8 to 12 repetitions for each of 8 to 12 exercises approximately 2 to 3 times per week; as with stretching, all major muscle groups should be included in the strength training programme.

In addition to improving physical performance and QOL, aerobic exercise may increase the likelihood that older adults will remain independent in activities of daily living. For most older adults, walking is the most suitable form of aerobic exercise, but stationary cycling and swimming are appropriate alternatives. Older adults embarking on an exercise programme should be advised to begin at a comfortable pace and exercise for a comfortable period of time. For HF patients, this may be as little as a few minutes of walking at a slow pace, but patients should not be discouraged by the fact that they are starting at a low level; indeed, data show that the greatest improvements occur in patients with the lowest baseline activity levels. Patients should exercise at least 4 to 5 days per week, gradually increasing the duration of exercise (but not the intensity) until it is possible to exercise comfortably and continuously for 20 to 30 minutes. Once this level of exercise capacity has been achieved, patients may consider further increasing the duration of exercise (e.g. up to 45 minutes) or gradually increasing the intensity. In either case, older HF patients should not exercise strenuously or to exhaustion. Additionally, patients should be instructed to stop exercising and contact their physician if they develop chest pain, undue shortness of breath, dizziness or syncope, or any other symptom that may indicate clinical instability. Finally, contraindications to exercise in elderly HF patients include decompensated HF, unstable coronary disease or arrhythmias, neurological or muscular disorders that preclude participation in an exercise programme, or any other condition that would render exercise unsafe.

End of life

The overall five-year survival rate for older patients with established HF is less than 50%; that is, the prognosis is worse than for most forms of cancer. Clinical features portending a less favourable outcome include older age, more severe symptoms and functional impairment, lower systolic blood pressure, lower LV ejection fraction, underlying CAD, hyponatraemia, anaemia, impaired renal function, and cognitive dysfunction. Older patients with advanced HF, as evidenced by NYHA class III–IV symptoms, have a one-year mortality rate of 25–50%; for these patients, HF can properly be considered a terminal illness. In addition, all HF patients are at risk for sudden arrhythmic death, which may occur during periods of apparent clinical stability. For these reasons, it is appropriate to address end-of-life issues early in the course of HF management, and to reconsider these issues periodically as the disease progresses or when changes in clinical status occur.[5]

Although discussing end-of-life issues is often challenging for healthcare providers as well as patients and families, specific measures should be undertaken to plan for and facilitate end-of-life care.[5] These include the development of an advance directive and appointment of durable power of attorney. The advance directive should be as explicit as possible in defining circumstances under which the patient does not want to be hospitalized, placed on a respirator, subjected to other life-sustaining interventions (e.g. a feeding tube), or resuscitated. Since patients may alter their views about these issues as clinical circumstances evolve, it is important to maintain open communication throughout the disease process.

End-stage HF is frequently accompanied by considerable discomfort and anxiety, and data from the SUPPORT study indicate that most patients and families have concerns about the quality of end-of-life care.[31] A cardinal principle of end-of-life care is to provide adequate relief of pain and suffering through the judicious use of conventional therapies in conjunction with narcotics (e.g. morphine), sedatives (e.g. benzodiazepines), and other comfort measures.[32] Equally important is the provision of emotional support for the patient and family, assisted by nurses, members of the clergy, social service representatives, and other qualified healthcare professionals. In some patients with

Table 41.7 Effect of anti-hypertensive therapy on incident heart failure in older adults.

Trial	N	Age Range (yrs)	Reduction in Heart Failure
EWPHE	840	>60	22%
Coope	884	60–79	32%
STOP-HTN	1627	70–84	51%
SHEP	4736	≥60	55%
Syst-Eur	4695	≥60	36%
STONE	1632	60–79	68%
HYVET	3845	≥80	64%

EWPHE, European Working Party on Hypertension in the Elderly; HYVET, Hypertension in the Very Elderly Trial; SHEP, Systolic Hypertension in the Elderly Program; STONE, Shanghai Trial of Nifedipine in the Elderly; STOP-HTN, Swedish Trial in Old Patients with Hypertension; Syst-Eur, Systolic Hypertension in Europe Trial

Table 41.8 New approaches to the treatment of chronic heart failure.

Pharmacologic Agents
Neutral endopeptidase inhibitors
Endothelin receptor antagonists
Cytokine inhibitors
Calcium sensitizers
Therapeutic Angiogenesis and Anti-angiogenesis
Inhibition of Apoptosis
Gene Therapy and Pharmacogenomics
Hereditary disorders (e.g. cardiomyopathies, dyslipidaemias)
Modulation of signalling pathways
Targeted therapy based on specific genetic profile
Implantable Assist Devices
Cell Transplantation and Growth Factor Therapy
Xenotransplantation
Prevention of Cardiovascular Ageing

terminal HF, institutional or home-based hospice care may be appropriate.[32]

Prevention

In light of the high prevalence and poor prognosis associated with HF in the elderly, it is evident that more effective means for the prevention of this disorder are needed. At present, the most effective preventive strategies involve aggressive treatment of established risk factors for the development of HF, especially hypertension and CAD. Several studies have shown that even modest declines in blood pressure are associated with substantial reductions in incident HF among elderly hypertensive patients (Table 41.7). In the HYVET study (Hypertension in the Very Elderly Trial), for example, treatment of hypertension in patients 80 years of age or older was associated with a 64% reduction in incident HF over a median follow-up of 1.8 years.[33] Likewise, treatment of elevated cholesterol levels with an HMG-CoA reductase inhibitor has been shown to decrease incident HF following an acute coronary event. Similarly, it is likely that smoking cessation and effective control of diabetes will contribute to a reduction in HF.

Future directions

Current treatment of HF in the elderly is characterized by marked under-utilization of proven therapies, insufficient evidence to guide treatment in major patient subgroups (e.g. octogenarians and beyond, nursing home residents, patients with advanced comorbidities, and individuals with HFPEF), and inattention to critically important psychobehavioural issues (e.g. adherence, personal preferences and end-of-life care). Thus, there is a need for additional research aimed at developing more effective strategies for the prevention and treatment of acute and chronic HF in older adults.

As shown in Table 41.8, several new treatments for HF, both pharmacological and technological, are currently under investigation. While rigorous testing is essential for evaluating the impact of each of these new therapeutic modalities, there is hope that many of these interventions will make significant contributions towards reducing the burden of HF in our progressively ageing population.

Key points

- Age-related changes in cardiovascular structure and function coupled with the rising prevalence of cardiovascular diseases at older age lead to progressive increases in the incidence and prevalence of heart failure with advancing age in both men and women.
- Heart failure in older adults often presents with atypical symptoms and signs, such as altered sensorium, behavioural changes, anorexia, or gastrointestinal disturbances.
- Common comorbid conditions and geriatric syndromes frequently interact with heart failure leading to clinically significant alterations in the clinical manifestations and response to therapy in older patients.
- Management of heart failure with reduced ejection fraction is generally similar in older and younger patients, but treatment for heart failure with preserved ejection fraction remains largely empiric due

to the lack of proven benefit from standard heart failure therapies.

- Optimal management of heart failure in older adults, especially those with multiple co-existing conditions or social isolation, is best accomplished utilizing a multidisciplinary team involving a nurse coordinator, geriatric clinical pharmacist, dietician, social worker, and one or more physicians.

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CHAPTER 42

Cardiac surgery

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Introduction

The primary enabling technology that led to the exponential growth in modern cardiac surgery was the development of the heart-lung machine in 1953. Currently, Western economies' estimated needs are 1000 to 1300 cardiac operations per million population. Life expectancy in Western economies has increased significantly during the past 50 years; in Europe it is now 84 years for women and 77 years for men, and in 2008 approximately 18% of the European population were more than 65 years of age. Moreover, cardiovascular disease is the leading cause of morbidity and mortality in the elderly,[1] and it is estimated that 25–40% of octogenarians have symptomatic cardiac disease.[2] Hence the increasing numbers of elderly patients undergoing cardiac surgery (Figure 42.1).[3]

The elderly continue to enjoy an active lifestyle and not unexpectedly want a good QOL, and many feel that a high operative risk, namely death on the operating table is an acceptable alternative to increasing debilitating symptoms in the last few years of life. The decision when to 'offer' or 'deny' cardiac surgery should though be answered in terms of outcome, mortality and morbidity risk in relation to the expected improvement in QOL. Careful preoperative assessment of comorbid risk factors is also essential in the elderly, because of competing comorbid disease mortality risks.

Cardiac surgery outcome in terms of mortality has continually improved as a result of the development of less traumatic heart-lung machines, more effective myocardial protection strategies, and improved peri-operative care. The mean age of patients undergoing cardiac surgery is progressively increasing and many octogenarians are now successfully undergoing cardiac surgery. In the United Kingdom, 22% of patients undergoing heart surgery were over 75 years of age in 2008 compared to less than 9% in 1999 (Figure 42.1).[3]

The demographics of the octogenarian or older patient undergoing cardiac surgery differ to that of the younger patient group,[4] in that patients are more likely to be female (~45%), are less likely to have diabetes (~20%), smoke (~35%) or have chronic lung disease (~10%); these observations are possibly indicative that only in the absence of these risk factors is an individual likely to live long enough to become a nonagenarian.

Age *per se* is not a contraindication for cardiac surgery provided the elderly patient can be discharged without significant disability and loss of independence.

Cardiac surgery outcomes in the elderly

Mortality

The type of cardiac surgery done is customarily grouped in terms of isolated coronary artery bypass grafting (CABG alone), CABG with concomitant valve surgery (CABG + valve), valve repair or replacement alone (valve alone), and Other procedures. Notably, the type of cardiac surgery done changes in the elderly; isolated CABG is the more common procedure in patients under 75 years of age (64% of heart operations), whilst heart valve operations predominate in patients over the age of 85 years (69%) (Figure 42.2).[3]

The mortality of cardiac surgery increases with both the complexity of the required procedure as well as with increasing age. Nevertheless, the crude in-hospital mortality associated with cardiac surgery in patients older than 80 years of age has now decreased to approximately 5–9% for isolated CABG, 8–11% for combined CABG and valve surgery, and 5–7% for isolated valve surgery (Figure 42.3).[3] The lower aforementioned mortality range figures approximate that for patients electively admitted for surgery from home as opposed to patients undergoing urgent surgery because of the severity of their condition, who have a

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

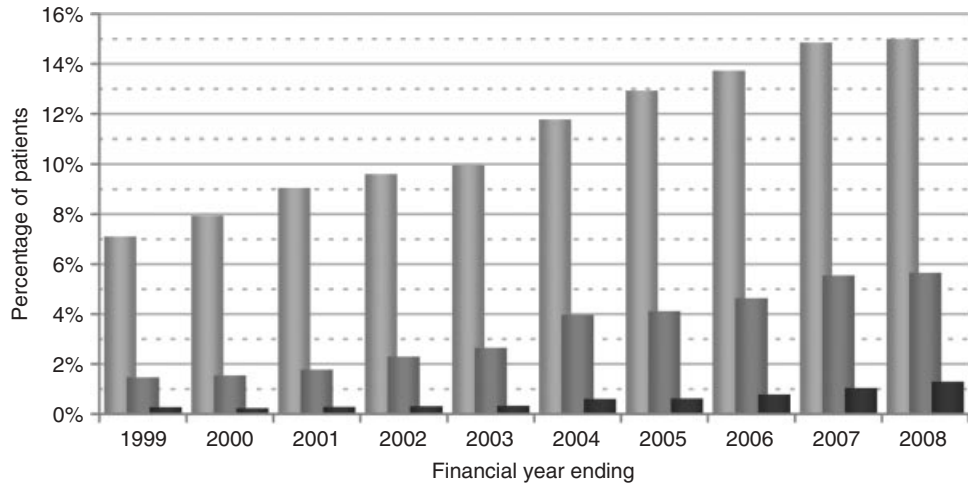

Figure 42.1 Trends in the relative proportions of older age groups by financial year, of 341 473 patients who underwent heart surgery in the United Kingdom. Age categories are, in increasing shades, 76–80 years, 81–85 years, and >85 years old. Reprinted from Bridgewater *et al.*[3] with permission from Dendrite Clinical Systems Ltd and The Society of Cardiothoracic Surgeons of Great Britain and Ireland.

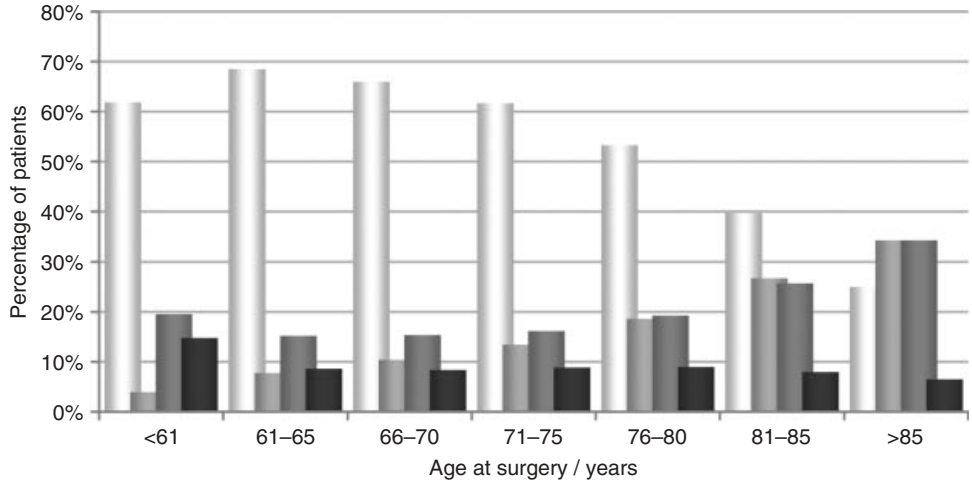

Figure 42.2 Type of cardiac surgery done in 184 461 patients undergoing heart surgery in the United Kingdom during the financial years 2004 to 2008 by patient age-group; isolated coronary artery bypass graft surgery (light shade bar), and in increasing shades combined CABG and valve surgery, valve repair or replacement surgery alone, or other procedures. Reprinted from Bridgewater *et al.*[3] with permission from Dendrite Clinical Systems Ltd and The Society of Cardiothoracic Surgeons of Great Britain and Ireland.

higher mortality. Nevertheless, elderly patients referred for cardiac surgery almost always have severe disease which if untreated would significantly reduce their life expectancy and result in a worse outcome than the aforementioned mortality rates.

Postoperative complications such as requirement for temporary haemodialysis (incidence: nonagenarian 9.2%, octogenarian 7.7% vs. 3.5% in younger age groups), stroke and prolonged ventilation all increase with age (Figure 42.4).[1] The average length of hospital stay following cardiac surgery in patients less than 60 years of age is 9 days but this increases to more than 15 days in patients older than 85 years.[3]

Nonetheless, the expected medium-term post-cardiac surgery actuarial five-year survival in the octogenarian is 60–75%, and with a significantly improved QOL.[5]

Pre-existing comorbid risk factors associated with increased mortality in octogenarians undergoing open-heart operations should be taken into account when advising patients of the risk of having surgery. These include New York Heart Association (NYHA) dyspnoea class III or IV, female gender, previous myocardial infarction, triple-vessel coronary artery disease, depressed left ventricular ejection fraction, chronic obstructive pulmonary disease, higher left ventricular end-diastolic pressure, preoperative intra-aortic balloon pump (IABP),

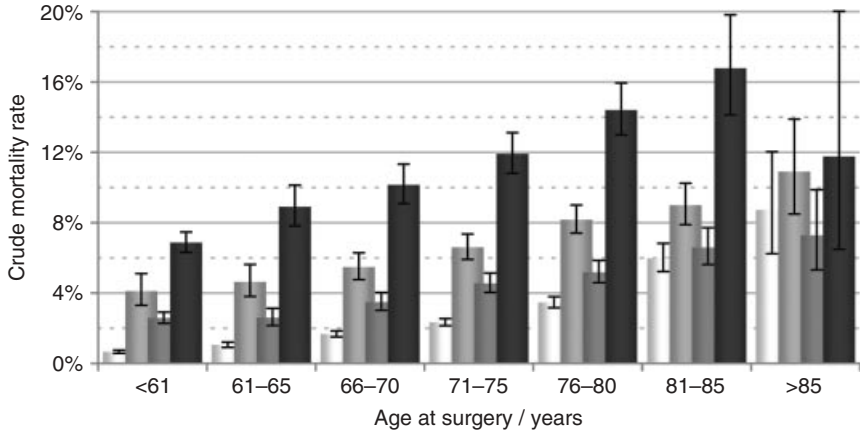

Figure 42.3 Unadjusted cardiac surgery mortality by patient age-group and procedure type in 184 461 patients undergoing cardiac surgery in the United Kingdom during the financial years 2004 to 2008; isolated coronary artery bypass graft surgery (light shade bar), and in increasing shades combined CABG and valve surgery, valve repair or replacement surgery alone, or other procedures. Reprinted from Bridgewater *et al.*[3] with permission from Dendrite Clinical Systems Ltd and The Society of Cardiothoracic Surgeons of Great Britain and Ireland.

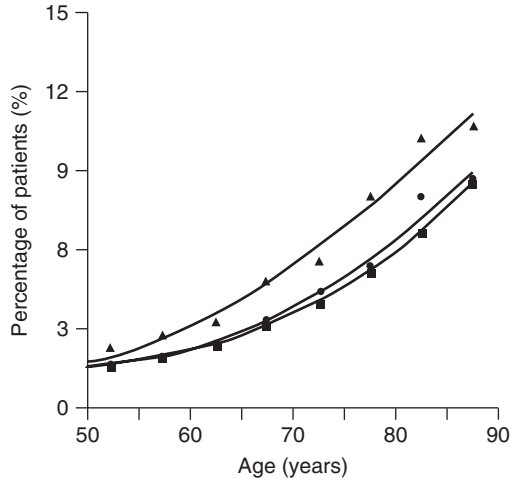

Figure 42.4 The rate of complications; in-hospital mortality (solid circles), neurological events (stroke, transient ischaemic attacks, or coma; solid triangles), and renal failure (oliguria with a creatinine $>1\,mg\,dl^{-1}$ or dialysis; solid boxes), by age in 64 467 patients following coronary artery bypass graft, with or without concomitant valve, surgery. Reprinted from Alexander *et al.*[1] Copyright 2000, with permission from Elsevier.

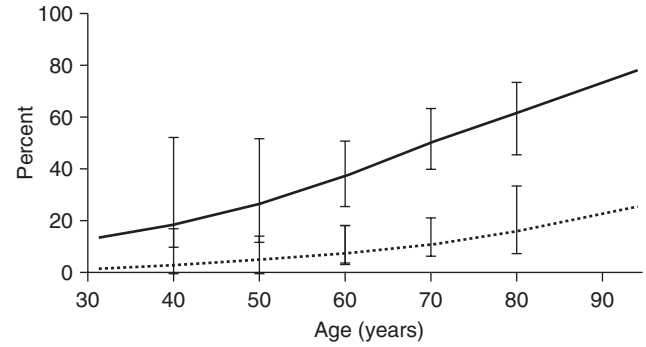

Figure 42.5 Probability of finding atheroemboli in organs, other than the heart or lungs, at 221 autopsies after cardiac operations for ischaemic or valvular heart disease, according to age and the presence of a preoperative history of peripheral vascular disease (solid line) or no history thereof (dotted line). Reprinted from Blauth *et al.*[6] Copyright 1992, with permission from Elsevier.

congestive heart failure, mitral valve operation, urgency of operation, chronic renal disease, as well as peripheral and cerebrovascular disease.[5]

Morbidity: Neurological dysfunction

The postoperative complication of greatest concern following cardiac surgery is a cerebrovascular accident (CVA), which is usually embolic in aetiology. A stroke significantly reduces postoperative QOL and is also associated with a high late mortality following hospital discharge.

The risk of a peri-operative stroke is higher in the elderly: being 13% in octogenarian compared to 4% in younger patients. Age-related morphological and physiological changes characterized by cerebral atrophy and diminished cerebrovascular reserve capacity, subclinical degenerative brain disease and severe atherosclerosis of the aorta as well as head and neck vessels are multifactor pre-existing comorbid risks contributing to the increased risk of postoperative neurological complications in the elderly (Figure 42.5).[6] Intraoperative manipulation of an atherosclerotic ascending aorta increases the probability of atheroembolism and consequent stroke. It is therefore important to identify elderly patients who are at high risk of sustaining a peri-operative stroke preoperatively in order to institute additional intraoperative protective strategies.[6]

Preoperative identification of patients with carotid artery disease is important, and our practice is to screen patients at risk for atheromatous disease with carotid duplex imaging (Table 42.1). Carotid artery disease is uncommon in the cardiac surgical patient who does not have coronary artery disease.

Patients scheduled for cardiac surgery who have coexisting symptomatic or asymptomatic carotid artery disease should then be assessed as to whether carotid

Table 42.1 Risk factors for internal carotid artery atheromatous disease.

- Carotid bruit
- Previous cerebrovascular accident
- Previous transient ischaemic attack
- Peripheral vascular disease
- Diabetes mellitus
- Left main stem coronary artery disease
  –If age greater than 65 years

artery endarterectomy is indicated either prior to or as a combined procedure with their cardiac surgery. A recent meta-analysis of combined versus staged procedure has shown that in stable cardiac patients the safer option is to perform carotid endarterectomy first followed by subsequent coronary artery bypass grafting.

The presence of severe ascending atherosclerotic plaque at the time of cardiac surgery is associated with a 10% incidence of peri-operative or late neurologic events, compared to 4% in patients with normal or only mild ascending aortic atherosclerosis. Intraoperative mechanisms of identifying ascending aortic atherosclerotic plaque are therefore useful in the elderly; either epi-aortic Doppler ultrasound or transoesophageal echocardiography. If significant atherosclerotic plaque is identified, then reducing ascending aortic manipulation such as off-pump surgery without any manipulation of the ascending aorta, cardiopulmonary bypass using single cross-clamp techniques, and the use of ascending aortic filtration devices are available techniques which can potentially reduce the risk of intraoperative atheroembolism.

More minor neurocognitive dysfunction such as memory loss and changes in visual acuity are also common after cardiac surgery and the aetiology is multifactorial. Pre-existing comorbid neurological risk factors, especially confusional states of indeterminate origin, should, however, be considered relative contraindications to cardiac surgery in the elderly, as undergoing open-heart surgery may aggravate them.

Assessment of the elderly patient for cardiac surgery

An improved longer-term prognosis is a frequent indication for cardiac surgery in younger patients; however in the elderly, this is less of an issue. Elderly patients must be assessed individually in terms of the natural history of their disease, symptoms thereof, comorbid diseases, current QOL, and the risk (mortality and morbidity) versus benefit (improved QOL) of any potential surgical intervention.

Operative risk: Estimated mortality for cardiac surgery

Mortality following cardiac surgery usually refers to either in-hospital, that is, deaths occurring within the base hospital during the same admission, or 30-day mortality, that is, deaths within 30 days of surgery. In the United Kingdom, the former definition is currently more commonly used.

Crude mortality fails as a comparative measure of quality between hospitals or surgeons, if there are major variations in case mix. A mechanism of risk stratification based on preoperative factors that increase operative mortality risks, such as age, is therefore essential if referral patterns, allocation of resources, and discouragement of the treatment of high-risk patients are to be avoided. Without risk stratification, surgeons and hospitals treating high-risk patients will appear, on the basis of crude mortality, to have worse results than others.[7]

The estimated risk of undergoing a given cardiac procedure is therefore determined from known preoperative risk factors and calculating the Euro Score (European System for Cardiac Operative Risk Evaluation Score), which is a weighted score that is used preoperatively to provide an estimated predicted operative mortality (Table 42.2).[7] The web site http://www.euroscore.org provides a free multilingual risk calculator for predicting cardiac surgical mortality, by both the additive and newer logistic Euro Score.

The additive Euro Score has been shown to provide a good correlation with actual observed mortality in the lower-risk groups, but is less accurate and tends to underestimate operative morality when the predicted operative mortality risk exceeds 9%. In the higher-risk groups, the alternative logistic Euro Score mathematical model appears to improve prediction. Although the original simple additive model remains a useful more user-friendly clinical tool to predict immediate operative risk (Table 42.2).

In the future, procedural one-year mortality or more will provide additional useful information for predicting 'true' outcome.

Benefit of surgery: Intended improved quality of life (QOL) following surgery

Increased survival is not the primary benefit of cardiac surgery in the elderly and should therefore not necessarily be the primary outcome indicator. Nevertheless, medium-term five-year survival for patients over the age of 80 years is remarkably good; isolated CABG ~70%, isolated AVR ~65% and isolated mitral valve repair ~72%.[3]

More important is assessing any expected improvements in QOL intended by a proposed cardiac surgical procedure,

Table 42.2 Weighted risk factors relevant to a specific individual patient are added and this then provides the Euro Score predicted mortality (%) for that patient to undergo the proposed cardiac surgical procedure (range 0–42%).

Risk factors and definitions	Weighted-score
Patient-related factors	
Age (years)	
60–64	1
65–69	2
70–74	3
75–79	4
80–84	5
85–89	6
≥90	7
Gender Female	1
Chronic pulmonary disease	
Long-term use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy (any or more of following)	
History of intermittent claudication, internal carotid occlusion greater than 50% stenosis, previous or planned abdominal aortic, limb or carotid vascular surgery	2
Neurologic dysfunction	
Severely affecting ambulation or day-to-day function	2
Previous cardiac surgery	
Requiring pericardial opening	3
Renal dysfunction	
Serum creatinine greater than $200\,\mu mol\,l^{-1}$ prior to surgery	2
Active endocarditis	
Still under antibiotic treatment for endocarditis at time of surgery	3
Critical preoperative state (any or more of following)	
Ventricular tachycardia, ventricular fibrillation or aborted sudden death preoperative cardiac massage, preoperative inotropic or intra-aortic balloon pump support, preoperative ventilation before arrival in anesthetic room, preoperative acute renal failure (anuria or oliguria <10 ml/hour)	3
Cardiac-related factors	
Unstable angina	
Rest angina requiring intravenous nitrates preoperatively until theater	2
Left ventricular dysfunction	
Moderate (left ventricular ejection fraction 30–50%)	1
Poor (left ventricular ejection fraction <30%)	3
Recent myocardial infarct	
Within 90 days of surgery	2
Pulmonary hypertension	
Pulmonary artery systolic pressure >60 mmHg	2
Operation-related factors	
Emergency surgery	
Carried out on referral before the beginning of the next working day	2
Other than isolated CABG	
Major cardiac surgery other than or in addition to CABG	2
Surgery on thoracic aorta	
For disease of ascending, arch, or descending thoracic aorta	3
Postinfarction ischaemic ventricular septal defect	4
Euro Score Predicted Mortality (%)	
Derived by the addition of the above relevant risk factor scores for each individual patient	Σ

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which is difficult. A perceived improvement in the NYHA dyspnoea score is not sufficient as it does not fully address the broader aspect of QOL and independent lifestyle.

Factors that impact on QOL are mostly physical rather then mental conditions. The SF-36 health survey questionnaire assesses eight general health concepts: physical functioning, bodily pain, role limitation because of personal or emotional problems, emotional well-being, social functioning, energy or fatigue, and general health perceptions. A study of octogenarians who had undergone cardiac surgery showed SF-36 scores equal or better than those of the general population of age greater than 65 years. Moreover, 84–94% of octogenarian operative survivors continue living on their own, and 83–98% indicated that they would in retrospect undergo cardiac surgery again because of the improvements in their lifestyle.[8]

To date preoperative QOL assessments such as the SF-36 questionnaire have not been used to guide preoperative decision-making. An alternative simpler assessment is the EQ-5D or EuroQol, which assesses the level of mobility, self-care, usual activity, pain or discomfort, and anxiety or depression, and may well assist in preoperative decision-making (Table 42.3).[9]

The elderly more frequently have additional coexistent medical conditions, which may frequently worsen, after cardiac surgery. Coexistent medical conditions must therefore be taken into account in terms of the patient's QOL. Diabetes mellitus with end-organ disease and renal failure are the most hazardous risk factors for a postoperative reduced QOL. Diabetes mellitus results in decreased mobility and chronic pain, whilst renal failure directly affects survival. Care should therefore be taken when selecting patients with those comorbidities for cardiac surgery.

A confounding factor in the assessment of the elderly for cardiac surgery, however, is that suboptimal timing of surgery, namely, excessively late referral for surgery, has a significant negative impact on both operative risk and late outcome.[10] The combined effect of delay, deteriorating cardiac status and exacerbating end-organ dysfunction (i.e. renal, pulmonary) may render an otherwise operable candidate beyond salvage.[8,11]

The elderly are more sedentary, may not notice milder symptoms, or may attribute symptoms to increasing age and may thus present late. Complete assessment on initial presentation is critical, and mild symptoms in the elderly should not preclude further investigations such as echocardiography and coronary angiography, in order to more accurately determine the presence and extent of any underlying cardiac disease. The decision whether to operate or not should be done without delay and not on a 'wait and see how symptoms progress' basis if the best surgical outcome is to be achieved.

Table 42.3 EuroQol questionnaire, which assesses five quality-of-life dimensions and perception of general and present health state.

EuroQol questionnaire
Mobility
I have no problem in walking about
I have some problems in walking about
I am confined to bed
Self-care
I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself
Usual activities (work, study, housework, family, or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities
Pain or discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort
Anxiety or depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed
Compared with my general level of health over the past 12 months, my health state today is:
Better
Much the same
Worse

Coronary artery bypass graft surgery

Coronary artery bypass graft surgery forms the majority of cardiac surgery today and was introduced as a therapeutic option in the early 1960s once myocardial ischaemia (angina pectoris or myocardial infarction) was shown to be due to narrowing of the coronary arteries from atherosclerotic plaque. Prospective randomized clinical trials in coronary artery surgery defined the indications for and benefits of CABG in both relieving symptoms and improving survival. These major trials showed that CABG increases survival in patients shown to have left main stem coronary artery stenosis, triple-vessel disease, or double-vessel disease on coronary angiography and in those with impaired left ventricular function or with left ventricular aneurysms. This applies equally in the elderly (Figure 42.6).[12]

CABG reduces the incidence of fatal myocardial infarction, relieves angina, and increases exercise capacity. However, isolated CABG does not improve symptoms of

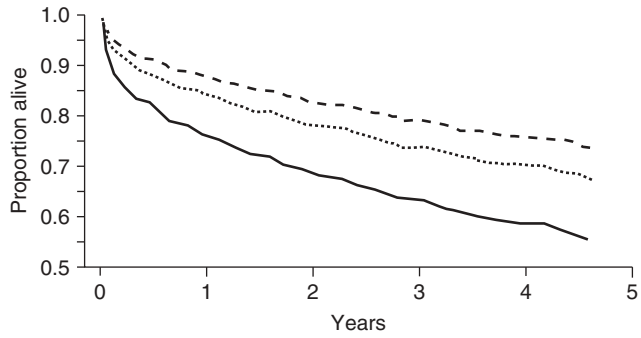

Figure 42.6 Risk-adjusted survival curves for 981 patients, 80 years of age or older, with ischaemic heart disease who underwent either revascularization by coronary artery bypass graft surgery (dashed line) or percutaneous coronary intervention (dotted line) versus continued medical therapy (solid line). Reprinted from Graham *et al.*[12] with permission from American Heart Association, Inc.

congestive heart failure, especially in the absence of proven hibernating or stunned myocardium.

Care though should be taken to not use the degree of symptomatic angina as the basis to refer an elderly patient for coronary angiography, as there is a poor correlation of the degree of angina with the degree of coronary artery narrowing. Up to 42% of patients with left main stem stenosis (the cohort of ischaemic heart disease patients at greatest risk of early death with continued medical therapy) will have only mild or no angina.[13] It is therefore important to make a distinction as to the indications of referral for further investigation as opposed to those for CABG surgery, which are not necessarily the same. Any recent change in angina symptoms should prompt a cardiologic assessment.

Delays in referring for diagnostic coronary angiography should not occur, as this may partly account for the increased prevalence of left main stem disease in octogenarians or nonagenarians (~32%) undergoing CABG as well as need for emergent surgery.[4] Left main stem stenosis of more than 50% remains an indication for CABG in the elderly even in the absence of severe symptoms, as less than 55% of medically treated patients 65 years or older with left main stem stenosis will survive for three years compared to an 87% survival for those undergoing CABG.[13]

In the United Kingdom, the operative mortality for isolated CABG in the elderly (age >75 years) has progressively decreased from 7.2% in 1999 to 3.3% in 2008, representing a reduction of ~50%.[3] Preoperative risk factors associated with increased operative mortality in nonagenarians from the US Society of Thoracic Surgeons database are shown in Table 42.4.[4] Similarly, in Europe, potentially delayed surgery, that is, waiting until the patient requires emergent surgery or reaches NYHA dyspnoea class IV, are important risk factors for an increased operative mortality in octogenarians.[2,11]

Table 42.4 Risk factors for operative mortality in nonagenarians undergoing CABG, listed in decreasing order of discriminatory importance.

Risk factors for CABG in Nonagenarians	Operative mortality
• Emergent surgery	26.6%
• Preoperative need for an IABP	26.3%
• Renal failure (Creatinine >2.0 mg%) or dialysis	20.90%
• Peripheral or cerebrovascular disease	10.60%
• Mitral insufficiency	7.2%

IABP, intra-aortic balloon pump
Source: Data derived from the Society of Thoracic Surgeons National Cardiac Database (1997–2000).[4]

A retrospective study of CABG surgery in octogenarians showed complete revascularization with CABG surgery to be more cost-effective than medical management; three-year survival of 80% in the surgical group versus 64%, QOL index of 84% in the surgical group (similar to an average 55-year-old in the general population) versus 61%, and lower cost per quality adjusted life-year gained in patients managed surgically.[9]

The overall outcome of CABG in the octogenarian can be improved by avoiding excessive delay prior to referral, frequently based on misperceptions that age is a contraindication for cardiac surgery.

Is percutaneous coronary angioplasty a better alternative in the elderly?

Percutaneous coronary revascularization is also associated with a better survival than medical therapy in the octogenarian with significant ischaemic heart disease (Figure 42.6).[12]

Perceived increased risks of surgery in the elderly should not, however, introduce a bias to opting for 'less invasive' percutaneous coronary angioplasty as being a better option in the octogenarian. Complications of coronary angioplasty increase disproportionately in octogenarians and can be associated with a high in-hospital mortality of 8.2%. Coronary anatomy is often more suitable for bypass surgery and incomplete revascularization is an independent predictor of both in-hospital and late mortality.[12]

Elective CABG surgery as opposed to percutaneous interventions is frequently a better option in nonagenarian patients, in the absence of significant associated comorbidity.[4] Coronary artery bypass grafting provides

a more favourable survivorship up to eight years after operation. Age alone should not be a deferent for aggressive treatment of coronary heart disease.

Use of the internal mammary artery as a conduit

CABG surgery was initially done using only reversed long saphenous vein as the bypass conduit between the ascending aorta and coronary artery, implanted distal to the flow limiting atherosclerotic plaque. However, the conduit that provides the best long-term patency is the internal mammary artery, and is today the conduit of choice as a pedicle graft to the left coronary system. Use of the internal mammary artery also confers an immediate survival advantage by reducing operative mortality.

Dissection of the internal mammary artery pedicle prolongs the operation time, is more technically demanding, and may be associated with increased postoperative bleeding, sternal infection in diabetics, and respiratory compromise. These reasons are therefore frequently cited to justify not using this conduit in higher-risk patients, such as the elderly. However, the use of an internal mammary artery has been shown to reduce mortality also in octogenarians undergoing CABG surgery (Figure 42.7).[1,14]

Newer techniques of harvesting the internal mammary artery by a skeletonized method can further reduce the risk of postoperative complications associated with its use. A high 71% use of internal mammary artery conduits in octogenarians as reported by Avery and co-workers, who also report one of the lowest operative mortalities of 2% in non-emergency octogenarian CABG, should be encouraged.[11]

The use of the internal mammary artery is beneficial in octogenarians by both reducing operative mortality and improving longer-term survival. Use of bilateral mammary artery combined with off-pump surgery may in selected elderly patients further reduce complications related to manipulation of highly calcified aorta. Age alone should not be a contraindication to arterial revascularization in selected patients.

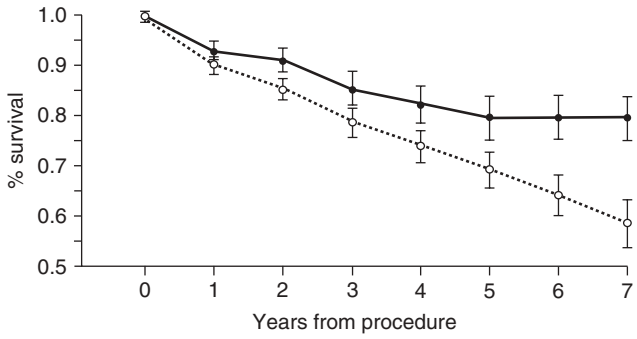

Figure 42.7 Actuarial survival rate of 487 patients 80 years of age or older who underwent coronary artery bypass graft surgery, and grouped according to whether they had received a left internal mammary artery graft to the left anterior descending coronary artery (solid line) versus those in whom only saphenous vein grafts (broken line) had been used. Reprinted from *Morris et al.*[14] Copyright 1996, with permission from Elsevier.

Antithrombotic therapy after coronary artery bypass graft surgery

Graft closure after CABG surgery is largely related to platelet aggregation and intimal hyperplasia. The current recommendation is therefore lifelong aspirin therapy at a dose of 325 mg day^{-1}. Aspirin doses of 75 mg have been suggested to be more effective then higher doses because low dose can 'spare' prostacycline and cause less gastrointestinal toxicity. A lower dose of aspirin has also been associated with diminished risks of major bleeding in acute coronary syndrome trials and this lower dose is now frequently prescribed.[15] It is important to commence aspirin therapy immediately postoperatively as early graft patency is not improved if therapy is delayed for 48–72 hours postoperatively.

Valve surgery

The proportion of patients undergoing cardiac surgery, requiring heart valve surgery (valve or valve + CABG) as opposed to isolated CABG surgery increases with patient age and approaches 70% in patients over the age of 85 years in the United Kingdom (Figure 42.2).[3] In the elderly though, successful cardiac surgery leads to greater improvements in perceived health status in valvular than in coronary artery disease patients.

Aortic valve replacement in the elderly

The predominant valve disease of the elderly is calcific degenerative aortic stenosis and accounts for 60–70% of the valve surgery caseload. Aortic valve cusps are calcified in 26% of adults older than 65 years and valve stenosis is observed in up to 5% of the population over the age of 75.[16] The development of symptoms (angina, syncope, or heart failure) identifies a critical point in the natural history of aortic stenosis, and symptomatic aortic stenosis without surgery is associated with only a 20% three-year survival.[17] In contrast, survival of the elderly patient after successful aortic valve replacement (AVR) surgery is similar to that of the natural population (Figure 42.8), as well as enabling them to return to an independent active life.[18]

Operative mortality for aortic valve surgery in the elderly approaches that obtained in younger patients and it is not until patients reach their 80s that age alone becomes a risk factor. Early mortality in octogenarians undergoing AVR

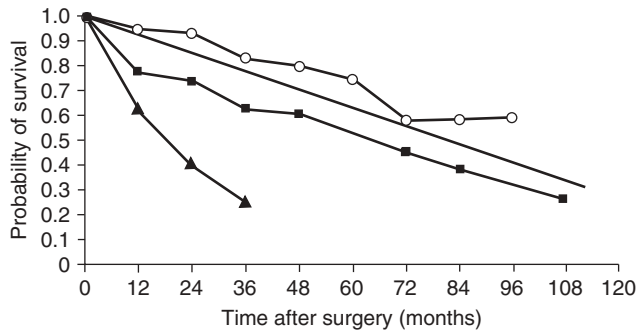

Figure 42.8 Comparative data between an unselected population of 80-year-olds in the United States (solid line), patients over 80 years of age with symptomatic aortic stenosis who did not undergo aortic valve replacement surgery (solid triangles) and 103 octogenarians with aortic stenosis who underwent aortic valve replacement with or without concomitant coronary artery bypass grafts surgery (solid squares). The survival curve of the aforementioned octogenarian patients who survived more than 30 days after surgery (open circles) is also provided. Reprinted from *Gilbert et al.*[18] with permission from the BMJ Publishing Group Ltd.

with or without associated CABG is between 5–11% in the UK.[3] Operative risk is primarily due to comorbid conditions, especially peripheral vascular disease, impaired renal function, previous cardiac surgery, poor left ventricular function and need for urgent surgery.[3,17] Once aortic valve disease is diagnosed in patients aged 80 or more, early referral for surgery should lead to the avoidance of hazardous developments (decreasing left ventricular function, loss of contractile reserve and the necessity for urgent surgery), and hence, to better postoperative outcomes.

Successful AVR surgery offers an excellent long-term outcome with long-term mortality being in most cases of non-cardiac origin. The medium-term five-year survival of octogenarians undergoing AVR is ~65% and for AVR combined with CABG ~55% in the United Kingdom.[3]

Asymptomatic aortic stenosis

The asymptomatic state is difficult to establish in practice in the elderly, due to a gradual decrease in activity or sedentary lifestyle.[16] Nevertheless, 'asymptomatic' aortic stenotic patients who should be referred for surgery include those with severe aortic stenosis (valve area $<1.0\,cm^2$ or an indexed aortic valve area $<0.6\,cm^2\,m^{-2}$ body surface area (BSA)), an abnormal response to exercise, left ventricular systolic dysfunction (left ventricular ejection fraction less than 50%), marked left ventricular hypertrophy ($\geq 15\,mm$ wall thickness), the combination of moderate calcification and a peak jet velocity $>4\,m\,s^{-1}$ as well as a rapid increase in peak aortic jet velocity of $\geq 0.3\,m\,s^{-1}$ within one year or patients with severe ventricular arrhythmias for which no cause other than severe aortic stenosis can be identified.[17]

Transcatheter aortic valve implantation (TAVI)

Octogenarians with symptomatic aortic stenosis who do not undergo surgery have only a 50% one-year survival.[18] However, a number of patients referred for surgery have significant comorbidities and therefore excessively high operative risks for open heart surgery. Percutaneous balloon valvotomy of elderly calcified stenotic valves have been poor; mortality 3–10%, strokes in 10–25%, as well as a 66% incidence of restenosis within six months.[19] Less than 20% of aortic valvuloplasty patients will survive a year and most of them will not improve symptomatically.

Newer percutaneous transcatheter valve replacement techniques were developed for patients turned down for conventional surgery and first used clinically in 2002. The current prostheses used consist of porcine or bovine pericardial valves mounted in either self-expandable nitinol or balloon expandable steel stents.[20]

The majority of transcatheter techniques are done without cardiopulmonary bypass and include either percutaneous transfemoral aortic valve implantation or transapical valve implantation through a mini-thoracotomy. The transfemoral arterial approach replaces the aortic valve retrograde via the femoral artery. Femoral artery size and tortuosity, severe peripheral vascular disease with atheromatous plaque makes this approach unsuitable in some patients. The transapical valve development uses direct balloon catheter implantation from the left ventricular apex, which is accessed through a small incision in the left side of the chest. A short period of rapid ventricular pacing is used with both techniques to decrease cardiac output during deployment of the prosthesis.

Published one-month mortality rates for TAVI range from 6–20%, cerebrovascular accidents in 2–10%, and residual paravalvular leaks in 50% of patients.[20,21] The degree of native valve insufficiency or new retrograde paravalvar leaks is though usually haemodynamically insignificant. The risk of strokes appears lower with the transapical technique by avoiding any manipulation in a calcified aortic arch, although mortality in some series has been higher with this approach.

Catheter-based aortic valve implantation is thus technically possible in elderly patients where conventional aortic valve replacement is not acceptable. However, one-year survival is between 54–80%, and is thus relatively poor in some series.[20,21] A one-year survival of less than 60% overlaps with that of patients treated conservatively and in addition at least one study has shown no significant improvement in QOL six months post-procedure.[21]

Debilitated patients often do not return to an active existence and additional comorbid pathologies with inherent competing mortality risks contribute to outcome. The appropriateness of an intervention directed solely to correcting aortic stenosis in patients turned down

for conventional surgery therefore needs very careful assessment.

Mitral valve surgery in the elderly

Elderly patients are regarded as higher-risk patients for mitral valve surgery; however, higher early and late mortalities are in part due to elderly patients being referred late (more than one year after presenting with significant symptoms) and undergoing surgery later in the history of their mitral valve disease.[10] Mortality doubles in patients undergoing any form of mitral valve surgery if over the age of 70 years compared to those less then 60 years.[3]

The predominant pathology in the elderly (developed economies) is either myxomatous degenerative or ischaemic-related secondary mitral valve regurgitation, and not unexpectedly in the former group, the elderly have significantly more associated coronary artery disease. The pathophysiology of degenerative mitral regurgitation is typically prolapse of the mitral leaflets as a result of elongated or ruptured chordae and mitral annular dilatation. In contrast, ischaemic regurgitation is usually due to restricted motion of the mitral leaflets as a result of segmental or global ventricular dilatation.

Chronic severe mitral regurgitation results in progressive and eventual irreversible left ventricular dilatation and myocardial failure (NYHA class III or IV) that is not reversed by eventual successful valve surgery (Figure 42.9).[10] Hence, early surgery (NYHA class I or II) is recommended for asymptomatic severe non-ischaemic mitral regurgitation regardless of age, if there are signs of left ventricular dysfunction (left ventricular ejection fraction less than 60%), AF or pulmonary hypertension (pulmonary systolic pressure >50 mmHg) and preserved left ventricular function, and especially if there is a high likelihood of mitral valve repair.[16]

The survival advantage of early surgery for severe mitral regurgitation is greater in the elderly than in the younger population.[10] Seven-year freedom from all-cause death in elderly patients (≥ 70 yrs) undergoing mitral valve surgery early (NYHA class I or II) was 77% versus only 44% if undergoing surgery late (NYHA class III or IV). In younger patients (<70 yrs) survival was 88% and 66% respectively.

Mitral valve replacement or repair

Conservative mitral valve repair rather than valve replacement should be done whenever feasible, as this is associated with both a lower operative mortality as well as improved long-term survival, regardless of presenting symptoms. Valve repair preserves the subvalvar apparatus and left ventricular function, thereby reducing mortality from myocardial failure. In addition, late thromboembolic and haemorrhagic complications are less frequent with mitral valve repair. Advances in surgical techniques including artificial Gore-Tex chordae have now made it possible for cardiac surgeons experienced in mitral valve repair to successfully repair more than 80% of degenerative and ischaemic regurgitant mitral valves. If mitral valve repair is not feasible, then replacement with a prosthetic valve, but with preservation of the subvalvar apparatus, is the next best option.

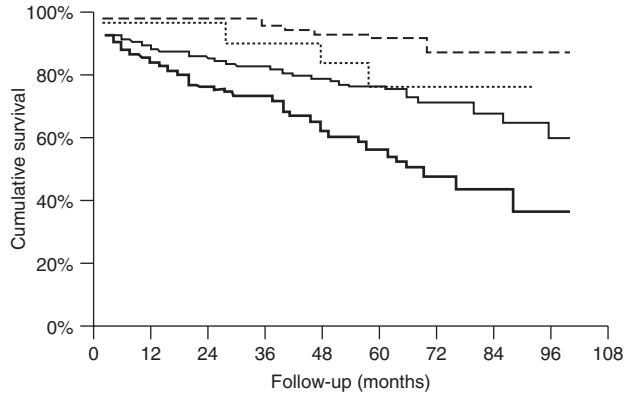

Figure 42.9 Long-term survival of 614 consecutive patients who underwent either mitral valve replacement or repair surgery, and grouped according to their preoperative NYHA dyspnoea class and age. NYHA class I or II sub-grouped according to age <70 years (dashed line) or ≥ 70 years (dotted line), as well as NYHA class III or IV subgrouped according to age <70 years (thin line) or ≥ 70 years (bold line). Reprinted from *Lee et al.*[10] with permission from ICR Publishers Ltd.

The preference for mitral valve repair as opposed to mitral valve replacement applies equally to both the young and elderly patient populations. The UK national data show both a halving of early operative mortality in octogenarians undergoing mitral valve repair compared to those undergoing mitral valve replacement, as well as an improved late survival.[3]

Choice of prosthetic valve: mechanical or biological in the elderly

A multitude of artificial mechanical heart valves have been developed, ranging from the initial obstructive 'ball and cage' valves to 'tilting disc' valves, and now 'bileaflet' mechanical valves made from titanium steel and pyrolytic carbon. Mechanical heart valves though have an associated lifelong thromboembolic risk from blood clots forming on the valve, which is the natural reaction of blood whenever it comes into contact with an artificial surface. This necessitates life-long anticoagulation with vitamin K antagonists (coumarin/warfarin), which in turn creates a risk of life-threatening major haemorrhage. A fine balance thus needs to be maintained for the rest of the patient's life, if mechanical prosthetic valves have been implanted; between too little

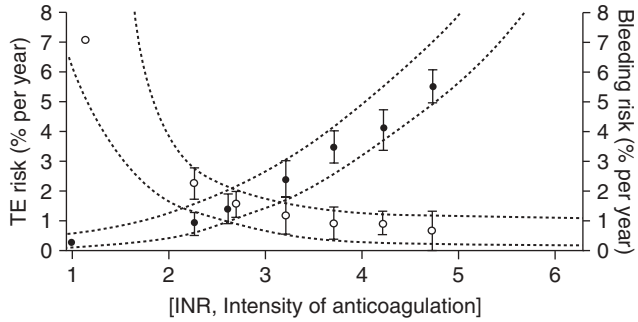

Figure 42.10 The incidence of thromboembolic (TE; open circles) and bleeding (solid circles) complications after 10-year follow-up, and grouped according to the average intensity of oral anticoagulation achieved by INR during the 10 years. The recommended target INR range was 3.0–4.5 in these patients with aortic mechanical St Jude heart valve prostheses. Reprinted from Horstkotte *et al.*[22] with permission from ICR Publishers Ltd.

anticoagulation which increases the risk of clot formation and thromboembolic ischaemic stroke, versus too much with its risk of anticoagulation-related haemorrhage and stroke (Figure 42.10).[22]

Constant lifelong monitoring and maintenance of the patient's serum international normalized ratio (INR) in the recommended range, which is discussed in more detail later in this chapter, is therefore essential in all patients receiving mechanical prosthetic valves. Contraindications to warfarin use therefore preclude the implantation of mechanical prosthetic valves (Table 42.5).[23]

Biological valves predominantly manufactured from bovine pericardium or porcine aortic valves have been developed as an alternative and do not require lifelong anticoagulation unless otherwise indicated. However, biological valves have a limited lifespan because of both calcium and non-calcium-related degeneration. Structural valve deterioration of bioprostheses is also higher in the mitral position than in the aortic position.[24] Fifty percent of 'first-generation' biological heart valves required replacement within 13 years of implantation. It has been thought that there is a reduced incidence of structural deterioration of bioprosthetic valves in the elderly; however, this has been shown to not necessarily be due to improved valve survival in the elderly but rather due to reduced patient survival from other causes. Nevertheless, current commercial, now improved 'third-generation' biological prosthetic valves, based on animal studies, are thought to have significantly improved valve survival compared to these older 'first-generation' bioprostheses. The major advantage of bioprosthetic valves in the elderly is that, unless otherwise indicated, lifelong anticoagulation with vitamin K antagonists is not required. The elderly (particularly >70 yrs) are at greater risk of thromboembolic and haemorrhagic complications secondary to coumarin therapy.[24]

The elderly patients would thus benefit from implantation of a biological as opposed to mechanical prosthetic valve and, therefore, either not requiring anticoagulation or alternatively at a lower therapeutic INR range if other indications for anticoagulation exist, because of the increasing comorbid pathologies associated with the elderly. Mortality from thromboembolic events and anticoagulation-related haemorrhage is three times higher in elderly patients over the age of 65 with mechanical prosthetic valves as compared to those with bioprostheses.[25]

The current recommendation is therefore to select a bioprosthetic heart valve for aortic valve replacements in patients equal or older than 60–65 years of age, and for mitral valve replacements in patients equal or older than 65–70 years (Figure 42.11).[24,26]

Table 42.5 Contraindications to coumarin/warfarin use.

The patient
- Comorbidity; including comorbid medical conditions, falls, frailty, exposure to trauma
- Impaired cognitive function
- Possibly housebound
- Poor expected compliance

The doctor
- Poor appreciation of drug interactions
- Inefficient organization of INR monitoring

The system
- General practice versus hospital facilities; for example, remote location, poor communication, and support
- Inadequate resources and facilities available.

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Combined coronary artery bypass graft and valve surgery in the elderly

Previous unproven dictums such as 'do as little as possible/only what is deemed essential' are slowly being disproved in terms of the extent of cardiac surgery undertaken. In CABG surgery, incomplete revascularization is an independent predictor of both in-hospital and late mortality.[12] The survival benefit of attending to coexistent moderate or more ischaemic mitral regurgitation at the time of CABG surgery is well established.

The supporting evidence for 'prophylactic' additional aortic valve replacement for moderate aortic stenosis (aortic valve area 1–1.5 cm^2, and more so if <1.3 cm^2, valve calcification or renal failure) in older patients (aged >60–65 yrs) already accepted for CABG surgery is becoming stronger,

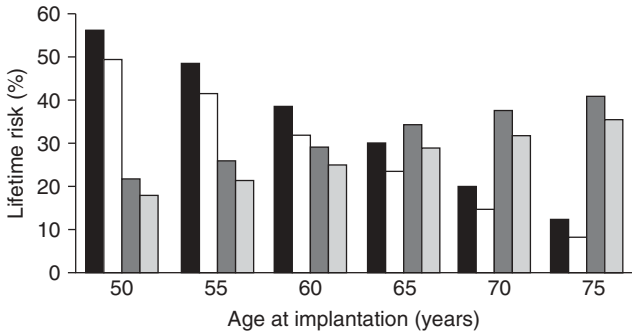

Figure 42.11 Microsimulation meta-analysis of the lifetime risk, according to the age at primary aortic valve implantation, of either structural valve degeneration of biological aortic valves without (solid bar) or with (open bar) concomitant coronary artery bypass graft surgery, or alternatively anticoagulation-related bleeding risks of mechanical aortic valves without (dark shaded bar) or with (light shaded bar) concomitant coronary artery bypass graft surgery. Reprinted from Puvimanasinghe *et al.*[26] Copyright 2003, with permission from Elsevier.

especially when considering the extremely high operative risk of subsequent re-operative valve procedures (~30% mortality), should it become necessary in an octogenarian. The presence of either aortic valve calcification or an aortic jet velocity of 3.0–4.0 m s^{-1} would suggest the likelihood of more rapid progression of aortic stenosis and therefore justification of a concomitant 'prophylactic' aortic valve replacement at the time of the initial CABG referral.

Acceptable surgical results are being obtained with these more complex procedures in the elderly, and should not therefore be denied to the elderly. Careful individual preoperative assessment as previously discussed is, however, essential.

Anticoagulation management in the elderly

Patients at risk for cerebral thromboembolic events include patients with mechanical prosthetic heart valves, AF, reduced left ventricular function (less than 35% ejection fraction), history of previous thromboembolism or hypercoagulable states and these patients should receive anticoagulation with vitamin K antagonists and their INR should be maintained in a range between 2.0 and 5.0.[27] Whether the target INR range is on the lower (INR 2.0–3.0), intermediate (INR 2.5–3.5), or upper (INR 3.0–4.5) side of this range will be dependent on the underlying thromboembolic risk, but will also influence the risk of anticoagulation-related haemorrhagic complications (Figure 42.10). The reason for providing a range is due to the difficulty of maintaining a 'constant' INR in any individual patient.

Warfarin, the most commonly used coumarin derivative, results in anticoagulation by inhibiting the synthesis of factors dependent on vitamin K, and has a considerable variability in its effects due to considerable pharmacokinetic and pharmacodynamic factors (Table 42.6).[23] This therefore demands frequent laboratory measurements of each individual patient's INR, and audits have even still shown that only 50% of patients are within their target range at any specific time point. The half-life of the vitamin K dependent factors range from 6–60 hours, thus any specific warfarin dose takes 2–3 days to produce an effect and this needs to be taken into account when managing warfarin dosage.

Patient self-management using their own 'point-of-care INR monitors' that are now available, especially in patients requiring lifelong anticoagulation, may offer the potential for both simplifying and improving oral anticoagulation management. A recently published meta-analysis of postoperative results and complications showed significant reduction in thromboembolic events, all-cause mortality and major haemorrhage in patients self-managing their INR.[28]

Table 42.6 This is only an illustrative list of interactive factors that influence the efficacy of warfarin.

Patient factors
Enhanced anticoagulant effect
Weight loss, increased age (>80 years), acute illness, impaired liver function, heart failure, renal failure, excess alcohol ingestion
Reduced anticoagulant effect
Weight gain, diarrhoea and vomiting, relative youth (<40 years), Asian or African-Caribbean background
Examples of some drug interactions with warfarin
Reduced protein binding
Aspirin, phenylbutazone, sulfinpyrazone, chlorpromazine
Inhibition of metabolism of warfarin
Cimetadine, erythromycin, sodium valproate
Enhanced metabolism of warfarin
Barbiturates, phenytoin, carbamazepine
Reduced synthesis of factors II, VII, IX, X
Phenytoin, salicylates
Reduced absorption of vitamin K
Broad-spectrum antibiotics, laxatives
Enhanced risk of peptic ulceration
Aspirin, non-steroidal anti-inflammatory drugs, corticosteroids
Thrombolytics
Streptokinase, tissue plasminogen activator
Antiplatelet drugs
Aspirin, non-steroidal anti-inflammatory drugs

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Anticoagulation for biological prosthetic valves

The current guidelines in patients with no other thromboembolic risk factors recommend temporary use of warfarin for only the first three months after biological valve implantation.[17] This is still controversial in patients with biological aortic valves, and thus, in these patients, either a temporary low-dose anticoagulation regimen (INR target range of 2.0–3.0), or antiplatelet therapy with aspirin (acetylsalicylic acid 75–100 mg day^{-1}) in patients not having reduced left ventricular ejection fraction (<35%), NYHA class IV, preoperative AF, or a paced rhythm can be used. After the first three postoperative months and provided there are no other thromboembolic risk factors, warfarin therapy can then be discontinued and replaced with aspirin 75–100 mg day^{-1}.[17]

Anticoagulation for mechanical prosthetic valves

Mechanical prosthetic valves in the aortic position (excluding first-generation Starr-Edwards, Lillehei Kaster, Omniscience, and Björk-Shiley valves) are considered to be less thrombogenic than in the mitral position (double the risk). Hence, patients with second- or third-generation mechanical prosthetic valves (St Jude Medical bileaflet, Medtronic-Hall tilting disc, CarboMedics bileaflet) can be maintained at an INR target range of 2.5–3.0 or 3.5 for the aortic position,[17,23,27] and at a slightly higher INR range of 3.0–3.5 or 4.5 for the mitral position.[23,27] The higher top endpoint should probably be used if there are additional thromboembolic risk factors; an enlarged left atrium (>55 mm in diameter), reduced left ventricular ejection fraction (<35%), dilated left ventricle (left ventricular end-diastolic diameter greater than 70 mm), AF, or previous thromboembolic events.

Patients with mechanical prosthetic valves require lifelong constant monitoring of their INR (initially daily then at least every 1–2 weeks depending on individual variance), as diet, coexistent diseases, medication, etc. interact with the efficacy of vitamin K antagonists (Table 42.6). Inadequate anticoagulation monitoring not only increases the risk of thrombosis, but also increases the risk of stroke (3–10%), major bleeding episodes (5%), non-disabling bleeding (14%), as well as recurrent thrombosis (11%). In the event that patients have evidence of prosthetic valve obstruction or thrombosis, they should be referred for emergent reoperation.[17]

Anticoagulant management of patients with mechanical prosthetic valves undergoing non-cardiac surgery

If it is necessary to interrupt oral anticoagulant therapy in patients with mechanical prosthetic heart valves, in preparation for elective surgical procedures, it is recommended to temporarily stop oral vitamin K antagonist therapy for 4–5 days preoperatively. Once the INR is less than <2.0, then either a continuous intravenous heparin infusion (prolonging the activated partial thromboplastin time (APTT) to twice normal) or subcutaneous low-molecular-weight heparin (100 U kg^{-1} every 12 hours) given to prevent thromboembolism.[23,27] The advantage of low molecular-weight heparin is the ability to provide this therapy on an ambulatory basis. However, its effects are only partially neutralized by protamine because of its higher anti-Xa activity, and it should therefore in turn be temporarily stopped 12–18 hours prior to surgery. Oral anticoagulation therapy is then recommenced the day after surgery or as soon as feasible in terms of intestinal function.

The aforementioned guidelines should also be used when patient's (requiring oral anticoagulation) INRs drop below their therapeutic range.

Parenteral vitamin K is not recommended in the treatment of non-life-threatening bleeding associated with warfarin use in patients with mechanical prosthetic valves because of the potential for induced hypercoagulable states.

Anticoagulation for atrial fibrillation (AF)

The efficacy of oral anticoagulation with vitamin K antagonists for preventing stroke in patients with AF has been well documented. Targeting the lowest intensity of anticoagulation to minimize the risk of haemorrhagic complications is, however, particularly important for elderly patients with AF, and, in these patients, an INR target ranging between 2.0 and 3.0 is recommended.[23,27] The risk of anticoagulant-related haemorrhage increases with age (1–2% patients per year, if below 60 years old).[17] Hence, in AF patients more than 75 years old, a target INR range of 1.5–2.5 albeit not as effective, or only aspirin treatment (325 mg day^{-1}) may be considered if there are no other indications for coumadin anticoagulation.

Non-pharmacological curative therapy for atrial fibrillation

Atrial fibrillation is the most common serious cardiac arrhythmia and is associated with a significant risk of cerebral thromboembolism. The prevalence of AF in the general population is approximately 0.4%; however, the prevalence increases markedly with age to approximately 9% in the 80–89-year-old population group. Furthermore, the risk of stroke associated with AF also increases with age from a 1.5% risk at age 50–59 years to 23.5% risk at age 80–89 years. Anticoagulation with warfarin reduces this risk of stroke but imparts a risk of anticoagulation-related haemorrhage and reduces patients' QOL.

The surgical Maze procedure developed by James L. Cox has been able to cure AF in up to 99% of carefully selected patients (predominantly patients with paroxysmal AF), and thereby has essentially abolished the risk of stroke associated with AF. Percutaneous transcatheter ablation of the pulmonary vein ostia, also in carefully selected patients with paroxysmal AF, now offers a less invasive approach and a success rate of approximately 75%.

Newer hyperthermic ablation devices including radiofrequency, microwave, ultrasound, and laser, as well as cryoablation devices have also now been developed to allow surgeons to do more rapid reproducible modified Maze procedures concomitant with other cardiac surgical procedures. Postoperative five-year freedom from AF in 'non-selected' patients with permanent AF of more than one-year duration, undergoing concomitant cardiac surgery, can now be expected in 42–87% of patients depending on underlying coexistent cardiac pathology.[29]

The non-pharmacological cure of AF is currently a rapidly developing field, and clear guidelines as to patient selection are slowly being developed. However, the elderly patient with AF who has the highest risk of stroke may potentially stand to gain the most from this emerging therapeutic option.

Thoracic aortic surgery

The incidence of thoracic aortic aneurysms and aortic dissections increases in the elderly and is a lethal disease. The five-year survival of patients not operated on is approximately 54%, and these patients have a 21–74% risk of acute rupture.[30]

The major factor influencing the risk of either acute rupture, dissection, or death is the diameter of the aneurysm at initial presentation; aneurysms greater than or equal to 6.0 cm in diameter have an annual risk of a negative outcome of 15.6% (Figure 42.12).[30] The risk of rupture with time increases 11-fold with aortic aneurysm size of 5.0–5.9 cm, and 23-fold with size of 6.0 cm or greater.[30] This needs to be compared with the risk of surgery, which has an operative mortality of 5–9% for elective surgery, but as high as 57% for emergency operations in the elderly.

The current accepted guidelines for asymptomatic aneurysms is to operate once an ascending aortic aneurysm diameter is 5.5 cm or more, or if a descending thoracic aortic aneurysm is 6.5 cm or more. However, a smaller diameter of 4.5–5.0 cm is used in patients with Marfan's syndrome or a family history of aortic aneurysms because of the higher incidence of rupture in these subgroups. Additional operative risk factors that need to be taken into account when assessing a patient for surgery on the descending thoracic aorta are the risk of spinal cord injury and paraplegia of 2–8%, which is related to the extent of the aneurysm and is highest in Crawford type II thoracoabdominal aneurysms.[31]

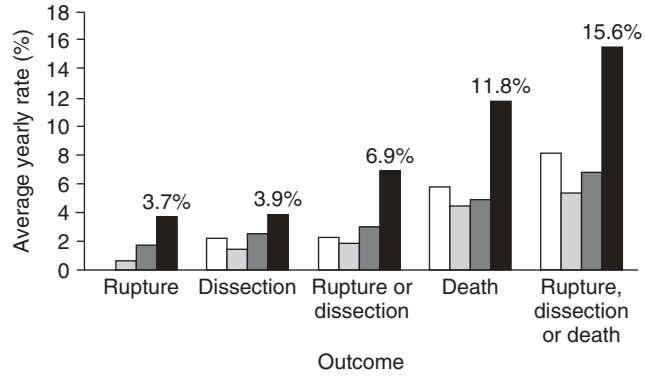

Figure 42.12 The average yearly rate (during the first five years after presentation), of negative outcomes (rupture, dissection or death) as a function of the initial thoracic aortic aneurysm (ascending, arch, descending or thoracoabdominal) size (maximal diameter); 3.5–3.9 cm (clear bar), 4.0–4.9 cm (light shade bar), 5.0–5.9 cm (medium shade bar), equal or greater than 6.0 cm (solid bar). Reprinted from Davies *et al*.[30] Copyright 2002, with permission from Elsevier.

In a large series (mean age 65 years), the risk of an adverse outcome (death, paraplegia, renal failure requiring haemodialysis or stroke) in elective thoracoabdominal aortic aneurysms was 13% and related to preoperative renal insufficiency, increasing age, type II extent, and symptomatic aneurysms.[31] An important conclusion of this study was that the development of any symptoms, no matter how mild or uncharacteristic, in patients with thoracoabdominal aneurysms requires immediate evaluation. The aneurysm must be considered the cause of the symptoms until proven otherwise as it indicates progression into a sub acute phase.

The main approach for these complex aortic repairs has been direct open repair, usually supported by deep hypothermic circulatory arrest. However, newer 'hybrid techniques' that combine surgical and endovascular approaches have been reported with lower morbidity and mortality.

These percutaneous inserted cloth-covered stainless steel stents were initially developed in 1969 and can now be inserted retrograde via the femoral artery into the abdominal and descending thoracic aorta, to seal off some aortic aneurysms. Current trials in appropriately selected patients have shown a procedural mortality of approximately 7% and five-year survival of 68%. In 'good surgical candidates' five-year survival of 78% was similar to conventional open surgical series, suggesting that cloth-covered stents are being increasingly used in patients possibly deemed unfit for conventional surgical interventions.[32] This technology is developing and it is hoped that improved stent design will reduce the risk of distal migration of stents and perigraft leakage, and become the preferred option in the elderly. The importance of the presence of an endoleak

is that it implies that there is no protection against acute rupture.

In patients judged to be poor conventional surgical candidates, five-year survival at 31% was, however, bleak and mainly due to coexistent disease. Moreover, QOL did not improve in patients asymptomatic in terms of their aneurysmal disease as opposed to their comorbid diseases.[32] Recent studies suggest that endografting can be performed as safely in elderly patients with no significant morbidity and mortality as in younger patients. However, at five years post-procedure the mortality in the octogenarian group is double (31.8% vs. 17.1%), although this increased mortality can be explained by the advanced age of the octogenarian who most likely died from other comorbidities. Increased age does not appear to be a risk factor for short- and mid-term morbidity and mortality for patients with stentable thoracic pathology. Older patients do as well after endostenting of the descending thoracic aorta and should be offered this less invasive approach.

Cardiac transplantation

The worldwide results of heart transplantation compiled by the International Society of Heart and Lung Transplantation Registry show that the current one-year and five-year survival following a heart transplant managed with modern immunosuppressive therapy is approximately 80% and 67%, respectively.[3]

A heart transplant is technically a relatively simple operation, but replaces a patient's original terminal heart disease with another disease; the disease of immunosuppression, which though is expected to carry a slightly better chance of survival. Nevertheless, constantly having to take drugs to prevent rejection of the new heart and balancing this against the risks of over-suppressing the body's defence mechanism which makes the patient prone to infection or cancer, becomes even more of an issue in the elderly.

In the United Kingdom, there is no prescribed age limit for acceptance onto a heart transplant programme; however, in practice, few patients above 65 years of age tend to be accepted. The international age distribution shows that less than 5% of heart transplants were in recipients aged 65 or more.[33] Availability of donor organs is the primary limiting factor for heart transplantation worldwide. Improvements in road traffic safety amongst others have resulted in a 40% reduction in the availability of cadaveric cardiothoracic donors in the United Kingdom over the past 10 years. Equitable allocation of donor hearts, an increasingly restricted national resource, is therefore necessary. In 2002–2003, only 32% of patients on an active cardiothoracic transplant waiting list (heart, lung or heart/lung) received an organ transplant.

An alternative option for patients with terminal heart disease not amenable to conventional cardiac surgery for whatever reason, which is now becoming available, is implantation of miniature blood pumps; totally implantable left ventricular assist devices. However, the current costs of these, what in the elderly will be 'destination therapy' devices will probably preclude universal access.

Conclusions

The elderly population has and will continue to increase and up to 40% of octogenarians have symptomatic cardiac disease. In the United Kingdom, 22% of patients undergoing heart surgery were over 75 years of age in 2008 and valve procedures predominate in octogenarians. Cardiac surgery mortality and morbidity outcomes have and will continue to improve and age itself is not a contraindication for cardiac surgery. The crude operative mortality for octogenarians undergoing cardiac surgery is currently less than 5–11% with postoperative five-year survivals of 60–75% being similar to the age-matched natural population. The major morbidity risk is that of peri-operative stroke because of the increased atherosclerotic vascular disease and can be as high as 13%.

Elderly patients must be individually assessed preoperatively in terms of the risk of the intended cardiac surgery; Euro Score-predicted mortality, versus the perceived benefit in their QOL; EuroQol, as well as the influence of other coexistent medical conditions. Although the prime indication for cardiac surgery in the elderly continues to be 'relief of symptoms', excessively late referral has a significant negative impact on both operative risk and late outcome. Mild symptoms need to be promptly investigated, if necessary by echocardiography and angiography, in order to more accurately determine the true extent of any underlying cardiac condition.

The unadjusted operative mortality for isolated CABG in the elderly (age >75 yrs) is ~3.3% and use of the internal mammary artery as a conduit is still recommended even in the octogenarian. Percutaneous coronary stenting or incomplete revascularizations are not necessarily better alternatives in the elderly.

Aortic valve replacement accounts for the majority of valve surgery in the elderly, and operative mortality is primarily related to comorbid conditions. Once again more complete assessment of the 'asymptomatic' patient is essential and early referral preferable. Replacement with a biological as opposed to mechanical prosthetic valve is recommended in the elderly because, unless otherwise indicated, lifelong anticoagulation is not required and the lifespan of current third-generation bioprostheses is greater than most elderly patient's projected lifespan. Percutaneous balloon aortic valvuloplasty is not considered to be a suitable alternative. However, transcatheter aortic valve replacement, usually without the use of cardiopulmonary bypass, is an emerging technique in elderly high-risk

patients deemed to be unsuitable for conventional heart surgery.

Chronic severe mitral valve regurgitation results in progressive irreversible left ventricular dysfunction and the survival advantage of early surgery (NYHA dyspnoea class II) is even greater in the elderly population, especially if mitral valve reparative surgery can be confidently undertaken.

Atrial fibrillation is an increasing problem in the elderly with an associated high risk of stroke. Developments in the non-pharmacological cure of AF are an attractive option in the elderly, who potentially have the most to gain in reverting to normal sinus rhythm and not requiring long-term anticoagulation, especially if concomitant cardiac surgery is already indicated.

Thoracic aortic dissections and aneurysms are more prevalent in the elderly, and untreated will rupture acutely in up to 74% of patients. In principle, patients who are symptomatic or with ascending aortic aneurysms greater than 5.5 cm or descending aneurysms greater than 6.5 cm should be referred for surgery. In appropriately selected patients, percutaneous inserted cloth-covered stents are becoming the preferred technique with the descending thoracic aortic aneurysms especially in the elderly.

Cardiac transplantation is not a realistic option in the elderly patient with terminal heart failure. However, new miniature fully implantable blood pumps may become an option in the future.

Key points

- Age is not a contraindication for cardiac surgery in elderly patients provided they can be discharged without significant disability and loss of independence.
- Elderly patients must be assessed individually in terms of the natural history of their disease, symptoms thereof, current quality of life, and the risk (mortality and morbidity) versus benefit (improved quality of life) of any potential cardiac surgical intervention.
- Referring elderly patients at an earlier stage of the disease process even with mild symptoms can improve the outcome of cardiac surgery in the elderly. Advising cardiac surgery as the last option and recommending a wait-and-see policy based on symptoms results in significantly poorer outcomes.
- Aortic valve replacement surgery if indicated, offers an excellent long-term outcome in elderly patients.
- Elderly patients benefit from implantation of a biological as opposed to mechanical prosthetic valve, if valve replacement is required, as bioprostheses do not require anticoagulation or, alternatively, at a lower therapeutic INR range, if other indications for anticoagulation exist.

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CHAPTER 43

Peripheral arterial disease

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Introduction

Peripheral arterial disease (PAD) occurs when blood flow reaching limbs is insufficient to fulfill the metabolic necessities of the tissue. This fact often comes from the presence of an occlusive arterial disease, the underlying disease process being atherosclerosis, which affects primarily, but not exclusively, the vascularization of the lower limbs.

Epidemiology

Risk factors for PAD

The factors leading to PAD are mainly the same as those leading to atherosclerosis, a process that directly or indirectly accounts for 70% of all deaths in people older than 70 years. These factors are multiple: genetic factors, metabolic diseases, inflammatory diseases, lifestyle and local and systemic conditions of the vascular system. Among these conditions and diseases are the major risk factors: age, type 2 diabetes mellitus, hypertension, dyslipidaemia, smoking, physical inactivity and abdominal obesity, age being the only non-modifiable factor.

The prevalence of PAD varies depending upon the characteristics of the population and the criteria used to define its presence.[1] There are two main methods to define PAD: the clinical one and the ankle-brachial index (ABI). The clinical method is based on the presence of the most classic symptom of PAD, namely intermittent claudication (IC), characterized by the presence of exertional calf pain that causes the patient to stop walking, resolves within 10 minutes of rest, does not resolve while the patient is walking, and does not begin at rest. The ankle-brachial index (ABI), a ratio of the systolic blood pressures in the lower and upper extremities obtained by Doppler, is the most widely used diagnostic test for detecting PAD. Among the participants in the Cardiovascular Health Study, an epidemiologic evaluation of 5084 community-dwelling men and women 65 years or older, the prevalence of PAD as defined by ABI was 12%, whereas only 2% of participants had IC.[2] The PARTNERS (PAD Awareness, Risk, and Treatment: New Resources for Survival) study, with 6979 men and women from primary care (aged 50–69 years with history of diabetes mellitus or cigarette smoking and 70 years or older), which also used the ABI as the diagnostic criteria, found a prevalence of 29%. Only 11% of these patients with PAD had IC.[3] The majority of the men and women diagnosed with PAD based on the ABI do not have classic symptoms of IC. The prevalence of classic symptoms (Table 43.1) varies from ~10–30% in patients with PAD based on the ABI value.

Age is the main risk factor for PAD. In fact, its prevalence increases dramatically with age. The Cardiovascular Health Study found a prevalence of PAD around 30% in men older than 85 years while it was lower than 10% in men ranging from 65–69 years old. The prevalence of PAD in women aged from 65–69 years old was lower than 5%, but exceeded 35% in those aged 85 or older. This association between older age and higher prevalence of PAD was also observed in both women and men with a history of heart disease and stroke.[2] Data from 2174 subjects aged 40 years and older from The National Health and Nutrition Examination Survey 1999–2000 show a PAD prevalence of 4.3% (95% CI, 3.1–5.5%) in the whole sample, but among those 70 years or over the prevalence was 14.5% (95% CI, 10.8–18.2%).[4]

Age is not only the most important non-modifiable factor which increases the risk of PAD two- to threefold. In addition, the pattern of the disease changes according to age: aorto-iliac disease occurs usually in younger subjects and is more rapidly progressive than distal disease.

Other risk factors besides age are smoking, diabetes, hypertension, dislipemia and black race. In the National Health and Nutrition Examination Survey 1999–2000,[4] more than 60% of individuals with PAD had hypercholesterolaemia, 74% were hypertensive, 26% had diabetes and 33% were current smokers. Approximately 95% had, at least, one of these cardiovascular risk factors and 72% had two or more. When adjusted by age and gender,

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 43.1 Stages and symptoms of PAD.

Fontaine's stages	
Stage	**Clinical**
I	Asymptomatic
IIa	Mild claudication (more than 150 metres)
IIb	Moderate–severe claudication (less than 150 metres)
III	Ischaemic rest pain
IV	Ulceration or gangrene

current smoking (OR 4.46; 95% CI, 2.25–8.84), diabetes (OR 2.71; 95% CI, 1.03–7.12), black race/ethnicity (OR 2.83; 95% CI, 1.48–5.42), low kidney function (OR 2.00; 95% CI, 1.08–3.70), hypertension (OR 1.75; 95% CI, 0.97–3.13) and hypercholesterolaemia (OR 1.68; 95% CI, 1.09–2.57) remained positively associated with prevalent PAD. After adjustment for smoking status, BMI, hypertension, hypercholesterolemia, diabetes and glomerular filtration rate, the smoking status (OR 4.23; 95% CI, 1.95–9.17), black ethnicity (OR 2.39; 95% CI, 1.11–5.12), diabetes (OR 2.08; 95% CI, 1.08–4.28) and low kidney function (OR 2.17; 95% CI, 1.10–4.30) remained significantly associated with the presence of PAD.

Smoking is a major and modifiable risk factor for PAD. Smoking not only predisposes to develop PAD but also increases its severity and affects the prognosis of revascularization interventions. In patients who smoke, PAD affects predominantly proximal arteries, especially the aorta and iliac arteries.[5]

The prevalence of PAD is approximately twice as high for individuals with diagnosed diabetes. Diabetes mellitus is not only a qualitative risk factor but also a quantitative one. In fact, glycaemic control is one of the strongest risk factors of illness: a positive, graded, and independent association between HbA1c and PAD risk has been described in adult people with diabetes.[6] This association is stronger for clinical (symptomatic) PAD, where manifestations may be related to the existence of microvascular disease, than for asymptomatic PAD. The glycaemic control is also associated with the worst consequence of this disease: amputation. In this regard, amputation is 10 times more frequent in diabetic than in non-diabetic patients. This suggests that efforts to improve glycaemic control in persons with diabetes may substantially reduce the risk of PAD. However, the efficacy of an intensive glycaemic control (reaching HbA1c values lower than 7%) to prevent PAD as compared with other less stringent therapeutic goals (~8%) is not established and, in fact, may have adverse consequences. Another important risk factor to develop PAD in diabetic patients is the presence of albuminuria, whatever its magnitude. Diabetes causes predominantly distal occlusive disease, including the arteries of the calves and feet.[5]

Although arterial hypertension contributes to the development of PAD to a lesser extent than either of the two previously mentioned factors, it is also a risk factor that must be controlled. There are limited data regarding the association between hypertension and PAD according to lesion localization.[5]

Black ethnicity is a strong and independent risk factor for PAD. At first, some epidemiological studies suggested a differential relationship between risk factors and prevalence of lower peripheral disease in people from different ethnicities. However, data from recent studies cannot explain the excess risk of PAD in black people by a higher prevalence of diabetes or hypertension, increased BMI or higher levels of some of the new cardiovascular risk factors (interleukin-6, fibrinogen, D-dimer, homocysteine). This suggests that unknown factors may account for the residual differences. In clinical series, PAD in blacks is associated with poorer prognosis after revascularization because of the greater presence of distal lesions involved.[5]

The Cardiovascular Health Study assessed the incidence rate of abnormal ABI over time in a community population (5888 participants, men and women 65 years and older, without PAD) and tried to identify what cardiovascular risk factors were predictors of ABI decline. ABI decline occurred in 9.5% of this elderly cohort over six years and was associated with modifiable vascular disease risk factors: current cigarette use (OR 1.74; 95% CI, 1.02–2.96), hypertension (OR 1.64; 95% CI, 1.18–2.28), diabetes (OR 1.77; 95% CI, 1.14–2.76), higher low-density lipoprotein cholesterol (LDL-C) level (OR 1.60; 95% CI, 1.03–2.51), and lipid-lowering drug use (OR 1.74; 95% CI, 1.05–2.89).[7]

Consequences of PAD

Peripheral arterial disease increases the risk of total mortality. Among these patients, more severe disease, as measured by the ABI, is associated with increased mortality. For example, mortality is higher in patients with an ABI less than 0.50 than in those with an ABI between 0.50 and 0.90. Traditionally, an ABI greater than 1.40 has been considered of little diagnostic value because it was believed that it indicates the presence of non-compressible lower extremity arteries. However, non-compressible arteries may be the manifestation of the presence of calcification of the media layer of the artery, a common condition in patients with diabetes and chronic kidney disease that is associated with increased mortality. Individuals with ABI values greater than 1.40 have a higher prevalence of intermittent claudication and atypical leg symptoms, suggesting an increased prevalence of PAD among these individuals. In fact, an ABI index higher than 1.40 is associated with an increased mortality. In this regard, The Cardiovascular Health Study

found an increase in total mortality in patients with basal ABI greater than 1.40 compared with a normal ABI. The magnitude of this increased mortality risk in people with an ABI greater than 1.40 was similar to that observed in people with an ABI less than 0.90. This suggests that across the spectrum of ABI values, the association between the ABI and mortality appears to be 'U' shaped.[1]

Peripheral arterial disease is a strong predictor of subsequent cardiovascular morbidity and mortality. Associations between PAD and cardiovascular mortality are independent of age, BMI, cigarette smoking, LDL-C, HDL-C, blood pressure, fasting glucose levels and history of angina, myocardial infarction, stroke or other heart problems. This association has been observed in multiple populations (clinical and community settings, general population and special groups like elderly or diabetic patients, subjects with and without classic intermittent claudication, etc). It has been reported over relatively short-term (3–4 years) and long-term (10 years) follow-up. Like the association between PAD and total mortality, the Strong Heart Study found a higher cardiovascular mortality risk if ABI was less than 0.90 or greater than 1.40, describing a 'U' shaped line too. PAD is associated with prevalent cardiovascular disease and adverse cardiovascular disease risk factor profiles. Prospective studies using the ABI show in people with a low ABI, a higher incidence of stroke (mainly in the elderly), fatal and non-fatal coronary disease, heart failure and a poor prognosis in all forms of cardiovascular disease. Because of that, identifying persons at both ends of the ABI distribution may be a useful method for cardiovascular risk stratification and may also be an indication for a comprehensive management of cardiovascular risk factors.[8] However, in the cardiovascular risk stratification, it is not just the grade of PAD that is important. The progression of PAD, measured as the changes in ABI over time, can add information in this evaluation of the cardiovascular risk. Criqui *et al*. demonstrated that progressive PAD (ABI decline >0.15) was significantly and independently associated with an increased cardiovascular risk.[9]

In addition to the classical implications of PAD on the cardiovascular disease, in the elderly PAD also plays a crucial role in determining an impaired functional status. Specifically, elders with PAD have lower physical activity levels, slower walking speed, poorer balance and poorer walking endurance. Data obtained from 1798 participants 60 years and older who participated in the population-based National Health and Nutrition Examination Survey,[10] showed several relevant findings about the relationship between PAD and physical function. Participants were asked about their dependence in performing several tasks (basic activities of daily living, instrumental activities, social activities, general physical activities and capacity to walk one-quarter mile and to walk up 10 steps). Trained health technicians measured ABI, maximal right leg force and gait speed. There were differences in both self-reported functional dependence and performance-based physical measures. Gardner and Montgomery[11] compared two groups of subjects 65 years and older, the first group with symptomatic PAD and the second one without illness. PAD patients had 28% shorter unipedal stance time, 86% higher prevalence of ambulatory stumbling and unsteadiness, and 73% higher prevalence of falling than non-PAD patients. Instability in patients with PAD was exacerbated in those with a worse ambulatory function and lower levels of physical activity. These findings remind us of the old scheme about the theoretical model of the pathway to late-life dependence proposed by Verbrugge.[12] He defined four related but different categories that represent the causal connection between pathology and actual dependence. These are: 'active pathology' (such as PAD), 'impairment' (such as low leg force or low ABI), 'functional limitation' (such as slow gait speed) and 'disability' (such as dependence in activity daily living). As a consequence, for a complete evaluation of an elderly patient with suspected PAD, performance-based physical measures (gait speed, strength, unipodal time, full tandem stance time, etc.) must be included.

Gardner *et al*.[13] followed 43 men limited by intermittent claudication (mean age, 69 years ±7) during 18 months to understand the natural evolution of physical performance in patients with PAD. They experienced a decline in six-minute walk performance, monitored and self-reported physical activity, physical performance, measured and self-reported stability and calf blood flow despite no change in ABI. While it may be assumed that all these changes could cause an impaired balance and a higher prevalence of falling, putting PAD patients at higher risk for serious injury, restricted physical activity, higher cost and more frequent hospitalizations, higher nursing home admissions and greater mortality, the actual clinical consequences and prognostic significance of functional impairment in persons with PAD was unknown until the study by McDermott *et al*.[14] They carried out a prospective observational study with 638 participants followed for a median of 50 months. Among PAD participants, the risk of mobility loss, measured as the hazard ratio (HR), in the lowest versus the two highest quartiles of baseline performance for the six-minute walk test was 9.65 (95% CI, 3.35–27.77, $p < 0.001$). For the Short Physical Performance Battery the adjusted HR was 12.84 (95% CI, 4.64–35.55, $p < 0.001$). They concluded that differences in the rate of mobility loss between PAD persons and healthy subjects appear to be primarily related to poorer lower-extremity performance at baseline. The measures of lower extremity performance predict risk of mobility lost and risk of mortality;[15] they are simple and easy to perform in the office. So, they can be used to identify PAD persons at highest risk of mobility loss.

The 'vulnerability' of these patients could suggest a possible relationship between PAD and frailty. In The Cardiovascular Health Study the ABI was inversely related to frailty status, in elderly people with or without clinical cardiovascular disease.[16] The prevalence of progressively lower levels of ABI increased in each level of frailty (non-frail, pre-frail, frail). These data, along with the other results in the CHS, suggest that cardiovascular disease appears to be an important, but not sole, contributor to frailty.

Finally, the association between PAD and other apparently unlinked diseases must be emphasized. This is the case for depression and dementia. An increased prevalence of depression in patients with PAD has been detected. One explanation could be that the functional impairment accompanying PAD affects QOL and may lead to depressive symptoms.

ABI is associated with the incidence of total dementia, vascular dementia and Alzheimer's disease,[17] as is shown in the data from the Honolulu-Asia Aging Study, a prospective community-based study of Japanese American men, older than 70 years at baseline. The analysis included 2588 men who were free of dementia at the first assessment, had an ABI measurement, and were examined up to twice more for dementia. After adjustment for education, year of birth, high blood pressure, BMI, diabetes mellitus, cholesterol concentration, smoking status, alcohol consumption and apolipoprotein E4 allele, a low ABI was associated with an increased risk of dementia (HR, 1.66; 95% CI, 1.16–2.37) and vascular dementia (HR, 2.25; 95% CI, 1.07–4.73). ABI was weakly associated with Alzheimer's disease (HR, 1.57; 95% CI, 0.98–2.53), particularly in the apolipoprotein E4 carriers (HR, 1.43; 95% CI, 1.02–1.96).

Despite what is claimed, the public is poorly informed about PAD. Current data suggest that PAD detection and treatment are lower than other forms of atherosclerotic disease, although there is evidence to support a prognostic significance and an impact on QOL comparable to other forms of cardiovascular disease.[18] As a consequence it is essential to make an active search of the disease. The Comprehensive Geriatric Assessment (including performance-based measures) plus ABI should be used to stratify the cardiovascular risk and to detect and prioritize the patients in whom an aggressive approach is needed.

Pathophysiology

Atherosclerosis is a long-lasting process of thickening and stiffness of the arteries, whose basic lesion is the atherosclerotic plaque. The evolution of atheroma involves several stages, which once breached, caused the harm. Unfortunately this complex process does not follow an ordered fashion, because even if the lesions develop gradually, the first symptom of many injuries occurs suddenly. Therefore, early diagnosis of atherosclerosis is important. To that end, it is essential to detect disorders associated with endothelial dysfunction and its progression toward atherothrombosis long before they are visible obstructive lesions, which highlights the importance of early detection and treatment of vascular risk factors. It must be remembered that vascular disease is not simply a local process in a concrete plaque, but this is a widespread process that affects the entire vascular tree. This concept has therapeutic implications because it calls for an integrated treatment. Another important aspect of the pathophysiology of atherosclerosis in the elderly, and more specifically of the endothelial dysfunction, is which processes that occur at the endothelium are due to physiological ageing and which ones to the presence of other cardiovascular risk factors. In fact, some of the mechanisms involved in the development of endothelial dysfunction are shared by both ageing and cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia),[19] as shown in Figure 43.1. Moreover, the mechanisms by which vascular risk factors lead to vascular disease may be different in the elderly.

Atherosclerosis is a universal process, although it shows some pathophysiological differences depending on the anatomical location of the occurrence. The atherosclerotic plaques located in the lower limbs are very fibrous and may result in strictures. When associated with a hypercoagulable state this gives rise to the acute event. By contrast, when present at the coronary arteries, the atherosclerotic plaque usually consists of a large extracellular lipid core and a large number of foam cells, coated with a thin cover susceptible to breakage, which is the ultimate cause triggering the acute event. Whatever the underlying process, the final consequence is the same: an imbalance between the needs of the tissues and the support of oxygen and nutrients. If this mismatch happens suddenly, as in the thrombotic event, it leads to acute ischaemia. If the establishment of the stenosis is gradual, allowing the development of collateral circulation, metabolic adaptation of the muscle mass involved and the use of non-ischaemic muscle groups, ischaemia may persist as a chronic state. From the pathophysiological point of view, one can talk about functional ischaemia when blood flow is insufficient to cope with the demand that involves the exercise but it is enough at rest. This functional ischaemia translates clinically into intermittent claudication. The critical ischaemia occurs when the flow is insufficient even at rest, appearing as pain and trophic lesions in the extremities. In this situation there is a need to intervene to restore an adequate blood flow, to avoid the risk of amputation. However, the symptoms will largely depend on the number of affected territories and the level of physical activity performed by each person.

The importance of inflammation in the genesis, progression and outcome of the atherosclerotic disease has emerged over the last two decades, adding to the classic

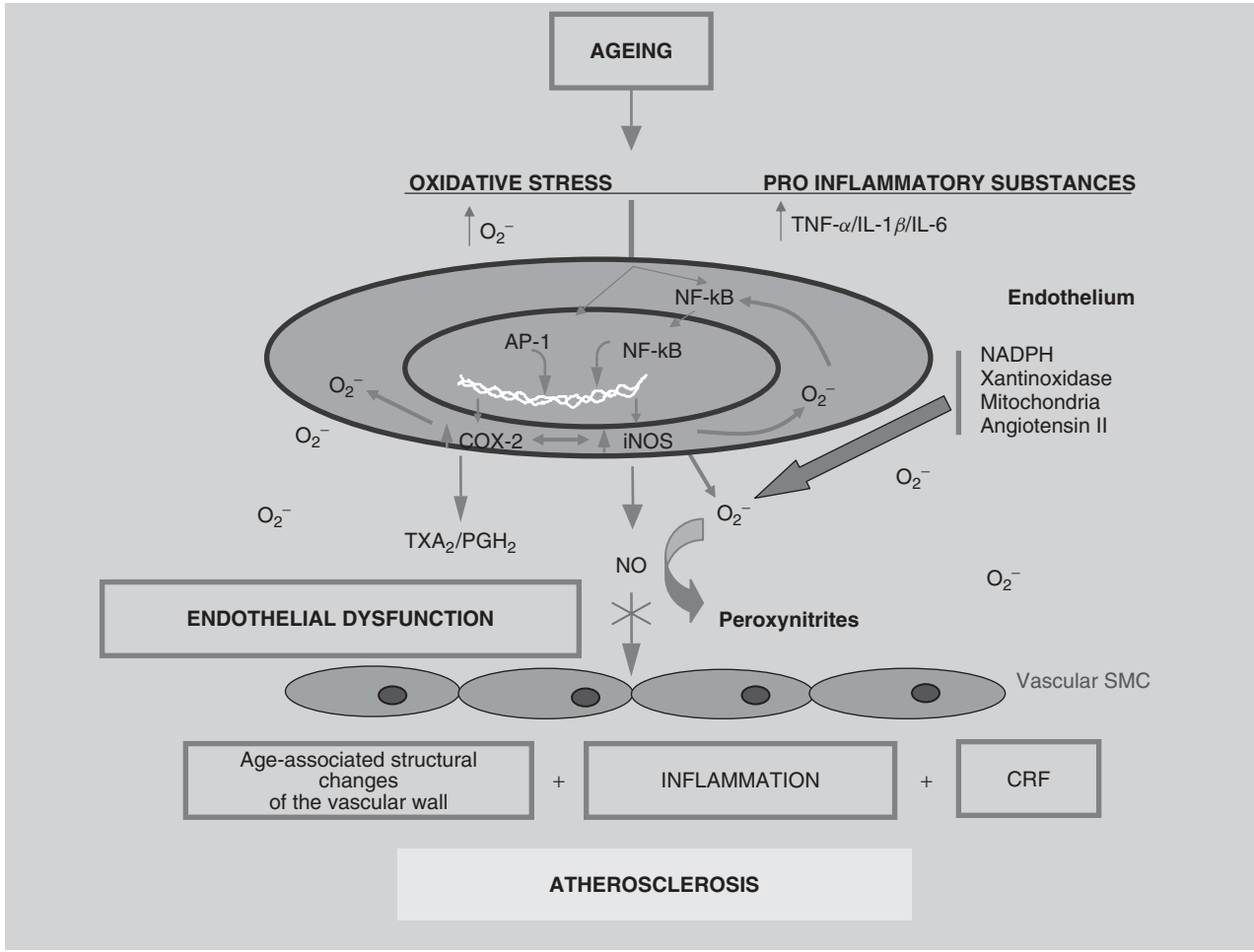

Figure 43.1 Mechanisms of endothelial dysfunction and atherosclerosis in ageing. COX-2, cyclooxygenase-2; CRF, cardiovascular risk factors; IL, interleukin; iNOs, inducible nitric oxide synthase; NO, nitric oxide; O_2-, superoxide anions.

concept according to which atherosclerosis is a mechanical accumulation of lipids and a fibrodegenerative response of the arterial wall by changes in its structure, leading to a progressive failure of tissue perfusion. Currently, atherosclerotis is regarded as a multifactorial disease where metabolic, inflammatory, haemodynamic and haemostatic factors are involved, with both local and systemic roles.

Glyco-oxidation contributes to the development of atherosclerosis in the below-the-knee peripheral artery tree in type 2 diabetes, and very probably also in elderly patients without diabetes. Advanced glycosylation end-products (AGEs) levels increase with ageing and in patients with diabetes. AGEs are elevated in type 2 diabetic patients with PAD as compared with diabetic patients without PAD and control subjects. More precisely, among AGEs components, pentosidine appears to be strongly associated with the peripheral artery status of diabetic patients. In addition, lipid oxidation, estimated by the serum levels of malondialdehyde (MDA), is associated with diabetic peripheral angiopathy. On the other hand, both TRAP and vitamin E levels, which estimate antioxidant capacity, are lower in type 2 diabetic patients with PAD than in those who are diabetic without PAD, and in healthy subjects.

As previously stated, inflammatory mechanisms are also involved in the pathogenesis of acute cardiovascular events. Elevated levels of inflammatory factors may encourage plaque instability and rupture. Higher levels of inflammation are associated with greater functional impairment and faster functional decline in persons with PAD. An explanation for these associations is not still available, but inflammation plays a key role in both atherosclerosis and sarcopenia, and in the age-related reduction in muscle mass and strength.

The presence of several cardiovascular risk factors, which act in a synergistic way, is the main condition for progression of the disease and amputation. In addition to these, there are other independent factors contributing to increased risk of amputation: sensory neuropathy, previous

minor amputations and the use of insulin. Furthermore, other factors very prevalent in the elderly (physical disability, loss of vision or a shortage of social resources), act as facilitators. As is the rule in geriatric medicine, the final outcome is the effect of the pathogenic concurrence of several factors, the main one being involvement of the peripheral nervous system, the microvascular damage and a superimposed infection.

Peripheral neuropathy diminishes algesic perception, putting the skin at risk for conditions such as pressure ulcers and muscle atrophy. As a consequence, changes in the points of support occur, placing pressure onto areas that are not prepared for it. So the heads of the metatarsals may suffer ischaemic necrosis, facilitating the development of osteomyelitis in the event of an underlying ulcer. The autonomic neuropathy facilitates the opening of artery-vein shunts and makes skin hydration difficult.

The relevance of the involvement of microcirculation has been widely discussed. Despite the existence of a thickening of the basement membrane, this factor does not appear to be of clinical significance in the absence of peripheral and autonomic neuropathy. Other factors, directly and indirectly related to vascular injury, cooperate in the development of clinically apparent damage: the ischaemia causes pain, especially in patients with high blood-glucose, difficulty in healing existing injuries and delay in the sterilization of infected lesions. Other mechanisms that can hinder healing include training AGEs or zinc shortfall related to its increased renal elimination in patients with poor glycaemic control. It is quite possible that this mechanism should be enhanced in the elderly. Ischaemia also hinders antibiotic response to infected ulcers.

Finally, other mechanisms associated with hyperglycaemia may participate in the pathogenesis of diabetic foot, but its role is more controversial. This is the case for the decline in chemotaxis, phagocytosis and bacterial lysis.

Diagnosis

Anamnesis and physical assessment

Diagnosis of PAD is based mainly on clinical evaluation and the patient's medical history. Patients frequently minimize symptoms, attributing them to normal ageing. Because of this an active search of intermittent claudication or atypical presentation of PAD must be carried out, distinguishing them from non-vascular causes (pseudoclaudication).[20] The 2005 ACC/AHA guidelines on PAD[20] and the 2007 TASC II consensus document on the management of PAD[21] recommend that the standard review of symptoms should include questions related to a history of walking impairment, symptoms of claudication, ischaemic rest pain, or non-healing wounds in patients ≥70 years of age, those ≥50 years of age with a history of smoking and/or diabetes, or, in TASC II, those with a Framingham risk score of 10–20% at 10 years. A careful history including a comprehensive geriatric assessment should reveal a functional impairment when this is the clinical presentation.

Clinical presentation

Adult patients with PAD often present with the classic symptoms of leg ischaemia. However, elderly patients are often asymptomatic, and, among symptomatic patients, atypical symptoms are more common than claudication.[3]

Many patients with PAD have unrecognized disease as illustrated by the following observations. In the PARTNERS programme cited above, around 45% of the patients with a new diagnosis of PAD had no history of leg symptoms and only 5.5% had classic claudication. In another study that included 239 men and women aged 55 and over with no history of PAD who were recruited from a general internal medicine practice, the ABI was abnormal (<0.90) in 14%. Most of these patients did not report exertional leg symptoms. However, they were not able to walk as far in six minutes as a group of patients without PAD (1362 vs. 1539 feet).

Older patients with PAD have atypical symptoms, usually focused on functional issues, mainly as a result of comorbidities, physical inactivity and alterations in pain perception. Functional capacity is diminished in some patients with PAD even in the absence of claudication, being the principal manifestation of the disease. In addition, a gradual decline in activity level or a progressive loss of independence in the activities of daily life may mask the symptoms of PAD in the elderly.

This issue was addressed in a study of 417 patients with PAD and 259 without disease who underwent measurement of ABI and assessment of functional capacity at baseline and one and two years later.[22] Patients with an ABI <0.50 had a significantly greater annual decline in six-minute walk distance than those with an ABI of 0.50 to <0.90 or those with an ABI of 0.90–1.50 (73 vs. 59 and 13 feet, respectively). In addition, patients with PAD who reported no exertional pain had a greater annual decline in six-minute walk distance than those with typical intermittent claudication (77 vs. 36 feet).

These findings suggest that activity level is an important factor in the evaluation of patients with PAD. Patients with evidence of PAD who report no or few symptoms should be asked about functional capacity and decline in activity over time.

Finally, some patients have atypical symptoms that may mimic other disorders[20] including nerve root compression, spinal stenosis and hip arthritis.

Physical examination

The physical assessment should include an exam with shoes and socks off, paying special attention to pulses (femoral,

popliteo, posterior tibial and pedal), bruits, hair loss, skin colour, temperature, ulcers and trophic skin changes.

We can measure the functional impairment using several validated tests and scores. Walking velocity, time to arise from a seated position or the standing balance score have been related to the presence of subclinical disease and its prognosis.[14,15] The most frequently suggested instruments are the Short Physical Performance Battery (SPPB) and the six-metre walking speed.

The Clinical Guidelines for Type 2 Diabetes Mellitus (European Diabetes Working Party for Older People 2011)[23] suggest that a Comprehensive Geriatric Assessment should be a routine measure in older people with type 2 diabetes at diagnosis and at regular intervals, and recommend as a minimum an annual inspection of the feet by a healthcare professional, including a vascular and neurological examination, even if no symptoms are present. When available, an ABI determination should be done (see below).

Detection of asymptomatic PAD has value because it identifies patients at increased risk of atherosclerosis at other sites. As many as 50% of patients with PAD have at least a 50% stenosis in one renal artery. Thus, patients with asymptomatic PAD, most often detected by ABI, should be assessed to detect clinically significant atherosclerosis in other vascular territories apart from the legs.

Non-invasive tests

These tests help to establish an accurate diagnosis of PAD, to quantify the severity of the disease, to localize the stenosis, to organize a treatment plan and to determine the progression of the disease or its response to treatment.

A variety of non-invasive examinations are available to assess the presence and degree of PAD. They include ABI, exercise treadmill test, segmental limb pressures, segmental volume plethysmography, and ultrasonography. Magnetic resonance imaging may become an important non-invasive method for assessment; however, at the present time costs and time considerations limit its use as a routine screening modality. The two most used methods in the clinical setting are the ABI and ultrasonography.

A relatively simple and inexpensive method to confirm the clinical suspicion of arterial occlusive disease is to measure the resting systolic blood pressures in the ankle and arm, and calculate the ABI, which provides a measure of the severity of PAD.

Calculation of the ABI is performed by measuring the systolic blood pressure (by Doppler probe) in the brachial arteries and in posterior tibial or dorsalis pedis arteries (Figure 43.2). The highest of the four measurements in the ankles and feet is divided by the higher of the two brachial measurements. Depending on the value of this index, several categories are defined:

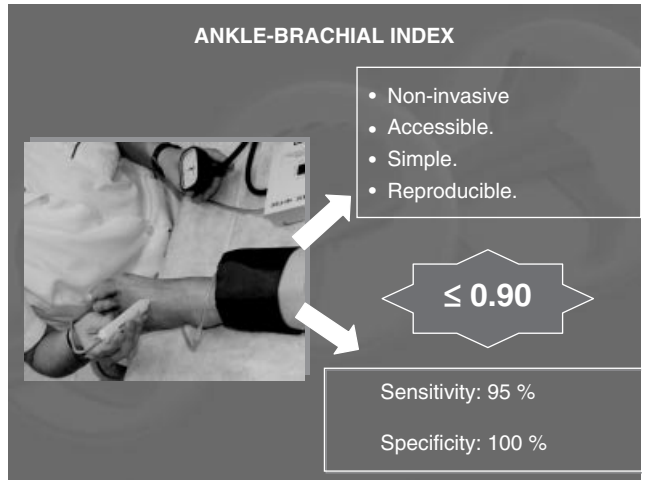

Figure 43.2 Measurement and diagnostic characteristics of the ankle-brachial index (ABI).

- Normal ABI: 1.0–1.3. Values above 1.30 suggest a non-compressible calcified vessel.
- ABI below 0.9 has 95% sensitivity (and 100% specificity) for detecting angiogram-positive PAD and is associated with ≥50% stenosis in one or more major vessels.
- ABI of 0.40–0.90 suggests a degree of arterial obstruction often associated with claudication.
- ABI below 0.4 represents advanced ischaemia.

If ABI is normal at rest but symptoms strongly suggest claudication, ABI and segmental pressures should be obtained before and after exercise on a treadmill.

As it has been previously stated, the ABI correlates with clinical measures of lower extremity function such as walking distance, velocity, balance and overall physical activity. In addition, a low ABI has been associated with a higher risk of coronary heart disease, stroke, transient ischaemic attack, progressive renal insufficiency and all-cause mortality.[8]

A potential source of error with ABI is that calcified vessels may not compress normally, possibly resulting in falsely elevated Doppler signals. Thus, an ABI above 1.3 is suspicious for a calcified vessel. An abnormally high ABI (>1.4) is also associated with higher rates of leg pain, cardiovascular risk and heart failure.

The examination of the lower extremity using the duplex ultrasonography (Doppler) begins at the common femoral artery and proceeds distally to the popliteal artery. An area of stenosis is localized with colour Doppler and assessed by measuring Doppler velocities at several arterial sites.

It has been suggested that the main purpose of duplex ultrasonography is to avoid the diagnostic angiography before intervention in patients with arterial disease proximal to the calf. A meta-analysis of 14 studies found that sensitivity and specificity of this technique for ≥50%

stenosis or occlusion were 86% and 97% for aortoiliac disease and 80% and 98% for femoropopliteal disease.

Invasive tests

At the present time, the contrast angiography is the 'gold standard' for the diagnosis of PAD. It is the definitive method before revascularization procedures. Although it is relatively secure, it is associated with a higher risk of medical complications (bleeding, infection, contrast allergy, etc.) than non-invasive techniques and should be performed only in selected patients (surgical patients).[20]

Treatment

The main aim when treating elderly people with PAD is to avoid the consequences of atherosclerotic disease in lower limbs and other vascular territories, and to prevent the functional decline associated with vascular disease.

Once the diagnosis is established, the patient can be treated medically by means of risk factor modification, exercise, foot care and drugs. If the disease progresses and/or the patient meets a number of established criteria, percutaneous intervention or surgery should be performed.

Risk factors modification

The principal risk factors for the development of PAD are ageing, cigarette smoking, diabetes mellitus, hypertension and hyperlipidaemia. With regard to the reduction of cardiovascular risk in elderly patients with PAD it must be stated that there is no concluding evidence about the relation between the control of risk factors and PAD prognosis. Nevertheless, the role of control of cardiovascular risk factors in the manifestations of atherosclerosis is well established. For this reason, treatment of cardiovascular risk factors is a priority in all patients with PAD, whatever their clinical manifestations.

Cigarette smoking

Cessation of cigarette smoking reduces the progression of disease as shown by lower amputation rates and lower incidences of rest ischaemia among those who quit. It is not clear whether smoking cessation reduces the severity of symptoms of claudication.

According to the recommendations of the 2007 TASC II consensus document, all patients should be strongly advised to stop smoking by their physicians and all patients should be offered nicotine replacement and group counselling sessions. Many patients may benefit from the addition of antidepressant drug therapy, but in older patients special attention should be paid to the adverse effects of this kind of drug on functional status.

Diabetes mellitus

There is no evidence on what is the best control level of cardiovascular risk factors in elderly diabetic patients with PAD. Because of this, treatment goals are similar to those in diabetic elderly patients.[20] No controlled trials have directly evaluated the effects of hypoglycaemic therapy upon the natural history of PAD. Aggressive control of blood glucose in both type 1 and type 2 diabetes reduces the risk of microvascular complications (e.g. nephropathy, retinopathy and neuropathy). However, in the Diabetes Control and Complications Trial of patients with type 1 diabetes, intensive insulin therapy had no effect upon the risk of PAD. The results were similar in the United Kingdom Prospective Diabetes Study in patients with type 2 diabetes.[24]

The 2007 TASC II consensus document on the management of PAD, recommends aggressive control of blood glucose levels with an A1c goal of <7% and as close to 6% as possible in adult patients. However, as previously stated at the beginning of this chapter, less stringent goals may be appropriate for elderly patients (around 7.5–8%, depending on the frailty status) and in those with comorbid conditions.[23]

Hypertension

Hypertension is a major risk factor for PAD. However, there are no data evaluating whether antihypertensive therapy modifies the progression of claudication. Nevertheless, hypertension should be controlled in these patients to reduce morbidity from cardiovascular and cerebrovascular disease.

There has been some concern in the past about the use of beta-blockers in the treatment of hypertension among patients with intermittent claudication, but there appears to be no adverse effect of beta-1 selective blockers on claudication symptoms. As a result, these drugs are not contraindicated in patients with PAD.[20]

There are no therapeutic groups that provide a differential benefit in these patients. Although the HOPE trial suggested that the angiotensin-converting enzyme (ACE) inhibitor ramipril provided added protection against cardiovascular events in patients with cardiovascular disease, including PAD, these benefits are likely to be a consequence of blood pressure reduction in this placebo-controlled trial, rather than a specific benefit of ACE inhibition although there is some evidence that ACE inhibitor therapy may increase walking distance in selected patients with PAD.

The blood pressure goal in these patients should be the same as that in patients with hypertension and established cardiovascular disease: below 130/80, as recommended by the American Heart Association and the European Society of Hypertension-European Society of Cardiology (ESH-ESC), or a higher goal of <140/90 mmHg if we adhere to the recommendations set by the 2007 TASC II consensus document. It must be highlighted than in the very old

person (≥80 yrs) with systolic hypertension there is no evidence about the benefits of decreasing blood pressure below 140 mmHg. By contrast, some studies have raised worries about the possibility of harm when blood pressure is reduced below that threshold.

Hyperlipidaemia

A number of cholesterol-lowering trials in patients with hyperlipidaemia and coronary and/or PAD have evaluated the effects of lipid-lowering therapy on PAD. A 2000 Cochrane meta-analysis of old trials mostly carried out before statins use, which specifically evaluated patients with lower limb atherosclerosis, concluded that lipid-lowering therapy reduced disease progression (as measured by angiography) and alleviated symptoms.

Subsequent studies confirmed these benefits in patients treated with statin therapy. Regression of femoral atherosclerosis, a lower rate of new or worsening intermittent claudication, and improvements in walking distance and pain-free walking time have all been described.

The Scandinavian Simvastatin Survival Study (4S), found that treatment with 20–40 mg day^{-1} of simvastatin reduced the incidence of new or worsening intermittent claudication by 38% (2.3 vs. 3.6% with placebo).[25]

Another randomized, double-blind trial included 354 patients with claudication attributable to PAD who were assigned to atorvastatin (10 or 80 mg day^{-1}) or placebo. At 12 months, there was a significant improvement in pain-free walking time with high-dose atorvastatin and in community-based physical activity with both doses of atorvastatin but there was no change in ABI.

With regard to the goals for lipid levels in elderly patients with PAD, there are no specific recommendations and the recommendations for adult patients[21] can be applied, with some caution. For instance, the recommendation for all patients with PAD to have their LDL-cholesterol lowered to <100 mg dl^{-1} (2.6 mmol l^{-1}), should be qualified in frail patients, where the risk of malnutrition is very high.

Exercise rehabilitation

Several studies have demonstrated the benefit of exercise rehabilitation programmes in reducing symptoms of claudication. A meta-analysis that included only randomized, controlled trials found that lower limb exercise produced a significant increase in maximum walking time (mean difference 6.5 minutes); the benefit was greater than that seen with angioplasty at six months (mean difference 3.3 minutes).[26]

The effect of upper limb exercise was assessed in a subsequent trial in which 104 patients with stable PAD were randomly assigned to twice weekly aerobic exercise training with upper limb or lower limb exercise or a non-exercise training control group. At six months, upper and lower limb exercise was associated with similar increases in claudication distance (51% and 57%), maximal walking distance (29% and 31%), and peak oxygen consumption.

There are several mechanisms by which exercise training may improve claudication, although the available data are insufficient to reach firm conclusions regarding their relative importance: improved endothelial dysfunction via increases in nitric oxide synthase and prostacyclin, reduced local inflammation, increased exercise pain tolerance, induction of vascular angiogenesis, improved muscle metabolism by favourable effects on muscle carnitine metabolism and other metabolic pathways, and reductions in blood viscosity and red cell aggregation.

A separate issue is whether patients with asymptomatic PAD benefit from exercise rehabilitation. This issue was addressed in a study of 156 patients with an ABI ≤0.95, most of whom were asymptomatic (81%), who were randomly assigned to one of three intervention groups: supervised treadmill exercise, lower extremity resistance training, or usual management (control group). At six months participants in the treadmill exercise group significantly increased in their distance walked (36 metres) during a six-minute walk test compared to those in the placebo group.[27]

Although less well studied, exercise may also improve survival. This issue was addressed in a prospective observational study of 225 men and women with PAD evaluated in whom physical activity was measured with a vertical accelerometer.[28] Patients were followed for a mean duration of 57 months at which time 75 patients (33%) had died. Individuals in the highest quartile of accelerometer-measured activity had a significantly lower mortality than those in the lowest quartile (HR 0.29; 95% CI, 0.10–0.83).

Exercise prescription must be done following some guidelines. Patients should be referred to a claudication exercise rehabilitation programme. These programmes consist of a series of sessions lasting 45–60 minutes per session, involving the use of either a motorized treadmill or a track to permit each patient to achieve symptom-limited claudication. The initial session usually includes 35 minutes of intermittent walking; after that, walking is increased by five minutes in each session until 50 minutes of intermittent walking can be accomplished, surrounded by warm-up and cool down sessions of five to ten minutes each. Ideally, the patient must attend at least three sessions per week, with a programme length greater than three months.

Foot care

The use of appropriate footwear to avoid pressure injuries, the use of moisturizing cream to prevent dryness and fissuring, daily inspection and cleansing by the patient and chiropody, are necessary measures to reduce the risk of skin ulceration, necrosis and amputation. Although these

measures are recommended based on the results of some works analysing their effects in diabetic patients, there are no studies evaluating their impact on elderly diabetic patients with PAD.

Pharmacological therapy

Drug therapy of claudication is aimed at symptomatic relief or slowing progression of the natural disease. A number of drugs have been evaluated but, as will be seen, the evidence of benefit is convincing only for antiplatelet agents, mainly aspirin and cilostazol.

Antiplatelet therapy

All patients with evidence for atherosclerosis in other vascular beds should be prescribed an antiplatelet drug. Asymptomatic patients without evidence for atherosclerotic disease elsewhere may be considered for antiplatelet therapy. Aspirin is the agent of choice; clopidogrel may be used if aspirin cannot be tolerated or in the subgroup of patients with symptomatic PAD. Anticoagulant therapy has not shown to improve cardiovascular outcomes in patients with PAD.

Cilostazol

It is a phosphodiesterase inhibitor approved by the Food and Drug Administration (FDA) for the treatment of intermittent claudication. It suppresses platelet aggregation and is a direct arterial vasodilator. The efficacy of cilostazol has been demonstrated in several studies and in a meta-analysis of eight randomized, placebo-controlled trials that included 2702 patients with stable, moderate to severe claudication.[29] In this meta-analysis, treatment with 100 mg twice daily for 12–24 weeks increased maximal and pain-free walking distances by 50% and 67% respectively. Benefit may be noted as early as four weeks.

Side effects noted in clinical studies included headache, loose and soft stools, diarrhoea, dizziness (increasing risk of falls) and palpitations, and is contraindicated in heart failure. It should be taken one-half hour before or two hours after eating, because high-fat meals markedly increase absorption. Several drugs such as diltiazem and omeprazol, as well as grapefruit juice, can increase serum concentrations of cilostazol if taken concurrently. All these features hamper its use in the elderly.

Pentoxifylin

It is a rheologic modifier approved by the FDA for the symptomatic relief of claudication. It is less effective than cilostazol.

Naftidrofuryl

Naftidrofuryl is a 5-hydroxytryptamine-2-receptor antagonist that is currently available only in Europe. The mechanisms of action of this drug are unclear but it is thought to promote glucose uptake and increase adenosine triphosphate levels. A meta-analysis of four trials showed an increase in the time to initial pain development on treadmill-walking over a three- to six-month period. This conclusion was also found in a 2008 Cochrane systematic review.[30]

The 2007 TASC II consensus document on the management of PAD concluded that naftidrofuryl (600 mg day^{-1} orally) can be considered for the treatment of intermittent claudication.[21]

The efficacy of other approaches, including other drugs like ramipril, verapamil, prostaglandins, and other treatments like antichlamydophila therapy or therapeutic angiogenesis, need confirmation in large trials (prostaglandins and antichlamydophila therapy) or are under investigation with controversial results (therapeutic angiogenesis).

Revascularization

There are two important criteria for revascularization: severe disability that limits the patient's ability to work or to perform other activities that are important to the patient, and failure (or predicted failure) to respond to exercise rehabilitation and pharmacological therapy. Endovascular or surgical revascularization therapy is reserved for patients whose functional capacity is compromised only by claudication (not for other comorbidities), patients who do not have a response to exercise and pharmacotherapy and patients for whom the risk-benefit ratio with revascularization is favourable.[20] These patients and the patients with critical and acute limb ischaemia should be referred to a vascular surgeon.

Acknowledgments

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CHAPTER 44

Venous thromboembolism

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Epidemiology and pathogenesis

Thromboembolism (venous, cardiac, or arterial) is the commonest cause of death, and a major cause of morbidity, in later life. Like cardiac and arterial thromboembolism, the incidence of venous thromboembolism increases exponentially with age approaching 1% per year by 90 years (Figure 44.1).[1] Almost half of cases occur between 60 and 79 years; and almost a quarter after 80 years (Figure 44.2).[1] This may reflect age-related increases in risk factors and comorbidities (Table 44.1), and in activation of inflammation, endothelium, platelets and coagulation[2,3] combined with age-related decreases in coagulation inhibition,[2,4] fibrinolytic activity and in general mobility.

Venous thromboembolism (VTE) may present as deep vein thrombosis of the leg (DVT) or pulmonary embolism (PE). Case-fatality is largely due to PE; and increases to over 10% in the elderly.[1] Treatment of VTE is also more hazardous in the elderly: the risk of major haemorrhage during anticoagulation increases by nearly 50% for each decade of age.[5,6] Hence prophylaxis of VTE is especially important in the elderly. Because about half of cases occur within three months of hospitalization, routine prophylaxis against hospital-acquired thrombosis is important.

Risk factors for venous thromboembolism in older patients are similar to those in younger patients, with the obvious exception of pregnancy and the puerperium (Table 44.1). There is increasing evidence that the pathogenesis of DVT involves a 'multiple hit model', which starts at conception with multiple, interacting, genetic predispositions (thrombophilias) which thereafter interact throughout life with acquired risk factors which may precipitate thrombosis (Figure 44.3). Once venous thrombosis has occurred, it acts as a strong predictor of the risk of recurrence, especially if idiopathic.

Genetic thrombophilias

Genetic thrombophilias should be suspected clinically if there is a past history, or a family history in blood relatives, of 'premature' (e.g. onset before 40–45 years) DVT, PE or recurrent fetal loss (spontaneous abortion or stillbirth); if there is recurrent venous thromboembolism or thrombophlebitis; or if thromboembolism occurs at an unusual site (upper limb veins, retina, cerebral venous sinuses, mesenteric, portal, or hepatic veins).[8] Protein C or protein S deficiency may also present with coumarin-induced skin necrosis.[8] Congenital deficiencies of the three coagulation inhibitors (antithrombin, protein C, or protein S) are usually due to heterozygosity for autosomal dominant gene defects; they increase the risk of VTE about two- to threefold.[9] The low prevalence of these mutations in non-Western countries may explain their low incidence of DVT and PE.

DVT in the population is also associated with increased plasma levels of the von Willebrand factor – coagulation factor VIII complex;[9] and probably explains why non-O blood group increases the risk of VTE by about 80% (non-O blood group elevates plasma levels of this complex by about 30%).[10] Homozygous homocystinuria has long been recognized as a risk factor for premature arterial and venous thrombosis. More recently, hyperhomocysteinaemia has also been associated with increased risk of both venous and arterial thrombosis: this is partly due to heterozygosity for cystein synthase or methylene-tetrahydrofolate reductase (MTHRF) deficiency (whose cumulative prevalence in the general population is 0.4–1.5%) and partly due to deficiencies of vitamins (folate, cobalamine and pyridoxine) especially in the elderly.[11]There is much current interest in the possibility that dietary supplementation of these vitamins could have a major impact on venous as well as

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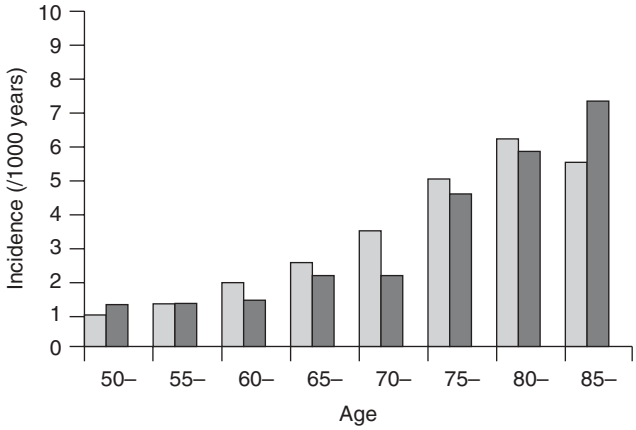

Figure 44.1 Incidence of first venous thromboembolism by age and sex. Rates are shown per 1000 per year, for men (striped bars), for women (solid bars). Reproduced from Rosendaal *et al.*[1] with permission from Wiley-Blackwell.

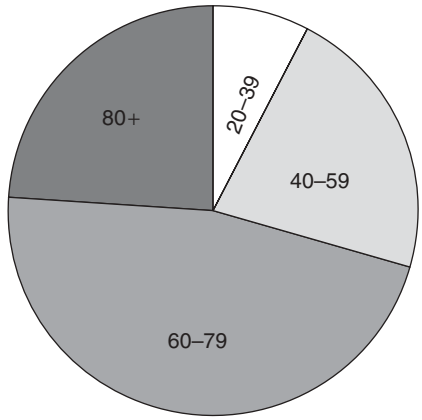

Figure 44.2 Age distribution of patients with venous thromboembolism. Percentage of patients by age group: 20–39 years, 7.5%; 40–59 years, 21.5%; 60–79 years, 45.9%; 80+ years, 23.6%. Reproduced from Rosendaal *et al.*[1] with permission from Wiley-Blackwell.

arterial thrombosis, particularly in the elderly; however, randomized trials have to date been inconclusive.[12]

Acquired risk factors

In recent years it has been increasingly appreciated that risk factors for arterial thrombosis (tobacco-smoking, obesity, diabetes and increased levels of blood lipids) are also risk factors for venous thromboembolism.[9] As with genetic thrombophilias, increased activation of blood coagulation is the most likely explanation.[9] Reduction in blood lipids by statin therapy appears to reduce the risk of VTE, as well as of arterial thrombosis.[13] Aspirin prophylaxis in high-risk persons reduces the risk of VTE, as well as of arterial thrombosis, by about 24%.[14]

Table 44.1 Risk factors for venous thromboembolism.

Patient factors	Disease or surgical procedure
Age	Trauma or surgery, especially of pelvis, hip, lower limb
Smoking	Malignancy, especially pelvic, abdominal, metastatic
Obesity	Heart failure
Blood lipids	Recent myocardial infarction
Immobility (bed rest over 4 days)	Paralysis of lower limb (e.g. stroke)
(Pregnancy)	Infection
(Puerperium)	Inflammatory bowel disease
Estrogen therapy	Nephrotic syndrome
Previous deep vein thrombosis or pulmonary embolism	Polycythemia
Genetic thrombophilias	Paraproteinemia
	Paroxysmal nocturnal haemoglobinuria
	Bechet's disease

Varicose veins increase the risk of postoperative DVT,[15] possibly because they may be a marker of previous (often asymptomatic) DVT in older persons. The increased risks of DVT and PE with increased estrogens, for example hormone replacement therapy,[16,17] suggest common mechanisms, including activated protein-C resistance, low levels of antithrombin and protein S, and high levels of factor IX.[17] These risks are increased in women with thrombophilias.[16,17]

Immobilization (at home or in hospital) in older persons is often due to medical illness (e.g. infection, malignancy, heart failure, myocardial infarction and stroke), trauma, or surgery. The cumulative risk of VTE increases with the duration of immobility, suggesting a role for venous stasis in the inactive leg in the pathogenesis of VTE. Venous stasis also increases in patients with paralyzed legs, heart failure, or polycythemia, which are also risk factors for VTE. Activation of blood coagulation also occurs following trauma, surgery and immobilizing illnesses including infection, malignancy, infarction and haemorrhage. The hypothesis that the combination of immobility and coagulation activation predisposes to DVT formation is supported by the prophylactic efficacy of both mechanical measures which increase leg vein blood flow, and antithrombotic drugs especially anticoagulants, and by the increased efficacy of combinations of mechanical with anticoagulant prophylaxis.

The elderly have a high prevalence of malignant disease, which activates blood coagulation and increases the frequency of both 'spontaneous' and recurrent venous thromboembolism. While the *relative* risk may be lower in patients aged over 70 years, about 5% of VTE events in

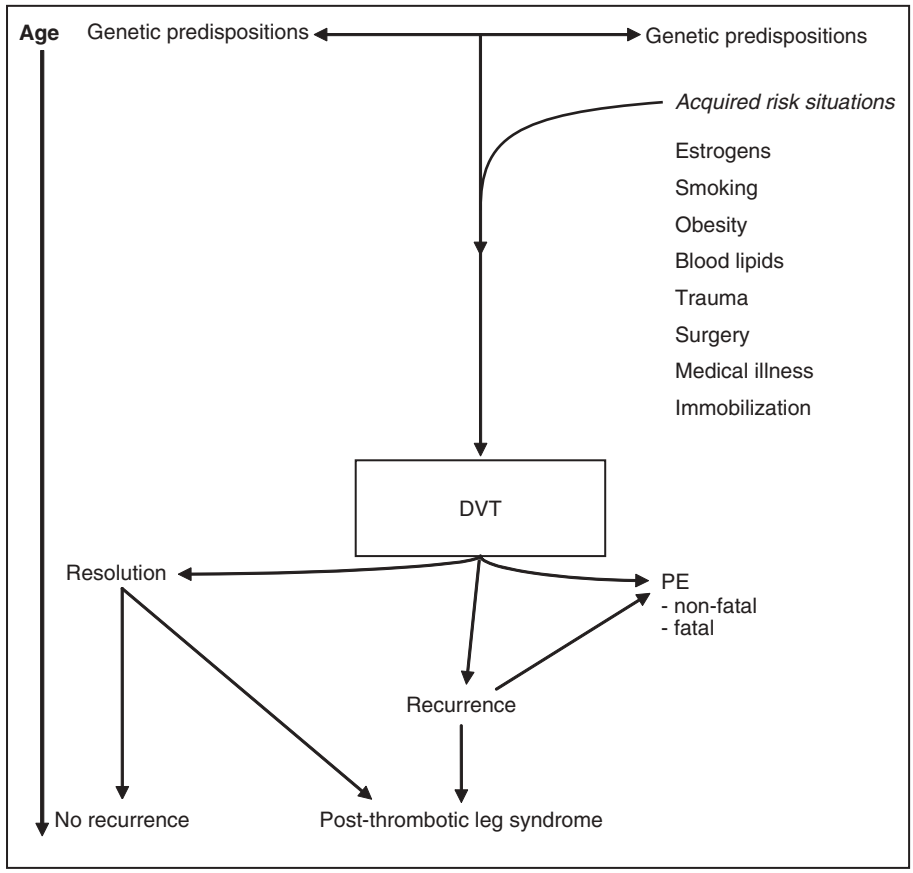

Figure 44.3 Multiple hit model for DVT.

the elderly can be attributed to cancer.[1] Whether or not a routine detailed work-up for cancer (beyond routine history, physical examination, routine blood tests and chest X-ray) improves prognosis is not yet established.

Less common acquired conditions which are associated with increased risk of venous thromboembolism include lupus anticoagulants, which are antiphospholipid antibodies and which usually occur in persons without systemic lupus erythematosis (SLE); inflammatory bowel disease, nephrotic syndrome, Bechet's disease, hyperviscosity (polycythemias, paraproteinemias), and paroxysmal nocturnal haemoglobinuria (Table 44.1).

Primary prophylaxis of VTE

In the great majority of patients dying from PE, previous venous thromboembolism was not diagnosed or treated. DVT is often non-occlusive and hence clinically silent prior to embolization; while non-fatal PE occurring prior to fatal PE may not be recognized clinically, especially in older patients who frequently have pre-existing cardiorespiratory symptoms, for example from heart failure or chronic obstructive airways disease.[18]

The clinical non-recognition of venous thromboembolism prior to fatal PE implies that its detection and treatment cannot have a major impact on its mortality: hence, identification of, and primary prophylaxis in, hospitalized patients (medical and surgical) at high absolute risk of DVT is required for its prevention. Increasingly, healthcare systems in developed countries (including the United Kingdom and North America) mandate routine assessment of all patients admitted to hospital for risk of hospital-acquired thrombosis.[19–22] A risk assessment tool is currently mandated in the United Kingdom.[21,22] Subcutaneous unfractionated or low molecular weight (LMW) heparin prevents about two in three cases of DVT; and also reduces the risk of PE (including fatal PE) in both medical and surgical hospitalized patients.[20–22] All hospital units and services should establish, (and regularly update), local protocols for prophylaxis, based on their national evidence-based guidelines and standards; and audit their performance.

Management of suspected DVT or PE

As with prophylaxis of venous thromboembolism, evidence-based guidelines for diagnosis and management

have been published in the United Kingdom and North America[22–24] from which local protocols, standards and audit should be developed. There is good evidence from randomized trials that full-dose anticoagulation (initially with heparins, followed by oral anticoagulants such as warfarin) is effective in secondary prophylaxis of recurrent thromboembolism, reducing morbidity and mortality. In patients for whom full-dose anticoagulants are contraindicated (usually due to high risk of bleeding), insertion of an inferior vena caval (IVC) filter should be considered to reduce PE risk. However, the costs and morbidity risks of both long-term anticoagulants and IVC filters require that they should be prescribed only to the minority of patients with clinically suspected DVT or PE in whom venous thromboembolism is confirmed by objective tests.

Venous thromboembolism should be suspected in patients with

1 congenital or acquired risk factors (Table 44.1) and

2 clinical symptoms or signs suggestive of either DVT – leg (usually calf, usually unilateral) pain, tenderness, swelling, oedema, warmth, distended superficial veins and/or PE – breathlessness, chest pain, cough, haemoptysis, wheeze, tachycardia, tachypnea, syncope, shock, or cardiac arrest.

In outpatients, the need for routine imaging studies can be reduced in the Accident and Emergency Department by clinical scoring, and a rapid test for fibrin D-dimer. In patients with a low clinical score and normal D-dimer, DVT and PE can be excluded. Other patients should receive heparin therapy (unless strongly contraindicated, e.g. by high risk of bleeding) until diagnostic imaging is performed.

For suspected DVT[22,23] *compressio*n *ultrasound* or *Duplex ultrasound scanning* are non-invasive, specific and sensitive to proximal DVT, but less sensitive to calf DVT. A negative ultrasound test does not exclude the presence of calf DVT, which in about 20% of patients may extend proximally over the subsequent few days and increase the risk of PE. Hence, a negative ultrasound test in patients with clinically suspected DVT should be repeated (usually after 5–7 days), or followed immediately by venography to exclude calf DVT.

Diagnosis of clinically suspected PE [22–24] includes

1 *chest X-ray and ECG* to exclude alternative diagnoses such as myocardial infarction, pneumothorax, or pneumonia;

2 *ventilation perfusion isotope lung scanning* which may be exclusive (normal) or diagnostic (high probability – 'mismatched' major lung segments that are ventilated but not perfused); but which in about 50% of cases is non-diagnostic (intermediate probability);

3 *computerized tomographic pulmonary angiography* (CTPA), contrast pulmonary *angiography* (invasive and not widely available), or *echocardiography* (suspected massive PE).

In contrast to unfractioned heparin, *LMW heparin*s do not require routine coagulation monitoring and have been shown in meta-analyses of randomized trials to have greater efficacy (lower rates of DVT extension, recurrence and mortality) and lesser risk of major bleeding than unfractionated heparin in the initial treatment of DVT.[22–24] Their efficacy as daily, unmonitored subcutaneous injections allows the possibility of outpatient treatment of acute DVT in many cases, provided this is acceptable to patients and their hospital and general practitioners. Many centres now have guideline-based local protocols for this.

*Oral anticoagulant*s (usually warfarin) are required as maintenance treatment following initial heparin treatment of DVT or PE, to reduce the risk of recurrence. They can be started as soon as objective diagnosis is obtained; concomitant heparin treatment should be continued until the target therapeutic range of the International Normalized Ratio (INR) (2.0–3.0) has been achieved for two consecutive days. The routine recommended duration of oral anticoagulant therapy following a first episode of VTE is at least three months.

Newer oral anticoagulants (e.g. dabigatran, rivaroxaban) have advantages, compared to warfarin, of efficacy in fixed dosage hence no need for coagulation monitoring; and lack of interaction with diet or other drugs. They are currently in evaluation.[25]

A significant percentage of patients develop recurrent VTE after discontinuation of oral anticoagulant drugs. Risk factors for recurrence include idiopathic presentation (no recent precipitating risk factors); male sex; continuing risk factors (e.g. estrogen therapy, cancer) and persistently elevated fibrin D-dimer levels.[26–28] Genetic thrombophilias do not appear useful in prediction of recurrence.[26,27] While clinical decision rules are under development and evaluation,[26,27] the decision on prolonged oral anticoagulant therapy, especially in older patients, often requires individualized assessment of risk factors, patient preferences and the risks and burdens of anticoagulants.[27] There are ongoing studies of antiplatelet agents in secondary prevention.[29]

Compression stockings should be prescribed routinely to be worn on the affected leg(s) during the day, long term, to reduce the risk of the post-thrombotic leg syndrome.[22,23]

Considerations in elderly patients

Practical considerations when prescribing oral anticoagulants to the elderly include:[6]

1 Sensitivity to the anticoagulant effect of a given dose increases with age: for example, an average warfarin dose of 4 mg day^{-1} was required in patients 74–90 years old to achieve the same target INR as an average dose of 8 mg day^{-1} in patients aged 19–35.[30]

2 Polypharmacy (including self-medications) increases the risk of drug interactions which alter oral anticoagulant effect, or which increase the risk of bleeding (e.g. aspirin and other non-steroidal anti-inflammatory drugs).

3 Increased prevalence of concurrent or intercurrent illness also increases risk of bleeding (e.g. severe anaemia, renal failure, gastrointestinal bleeding, haemorrhagic stroke, bleeding disorder).

4 Decreased compliance or decreased access to monitoring – whether performed by the general practitioner or hospital anticoagulant clinic – also increases risk of bleeding.

Key points

- Venous thromboembolism is common in elderly patients, especially with obesity, malignancy, heart failure, immobility, trauma, surgery and acute medical illness.
- Consider primary prophylaxis (low-dose heparin, aspirin, or stockings) in acutely immobilized patients, especially those with other risk factors, previous DVT or PE, or known thrombophilia.
- Diagnosis of suspected non-massive DVT or PE involves a formal clinical score and rapid D-dimer in outpatients; proceeding to initial heparin therapy and diagnostic imaging.
- If diagnosis is confirmed, oral anticoagulation with warfarin (target INR 2.0–3.0) is usually given for at least three months.
- Older patients are at increased risk of bleeding on oral anticoagulants.

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CHAPTER 45

Cardiac rehabilitation

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Cardiac diseases and rehabilitation services

Epidemiology

In 2001, cardiovascular diseases were still the first among the leading causes of death in men and women of all ages in the USA, with coronary heart disease (CHD) alone accounting for 54% of all cardiovascular deaths. The prevalence of cardiovascular diseases – including CHD, stroke and hypertension – increases with age up to more than 70% at age 75 years and older. A surveillance study performed by the National Heart, Blood and Lung Institute in 1987–2000 reported that the incidence of first heart attack is also increasing exponentially with age.[1]

Thanks to the remarkable advances in the management of acute CHD events, chronic heart failure (CHF) and cardiovascular risk factors, the specific mortality for heart disease has been declining continuously during the last two decades, especially among men. Furthermore, preventive medicine has shifted the age at which patients develop CHF but has not reduced, and indeed may have increased, its global epidemiological burden. As a consequence, growing numbers of cardiac patients currently survive longer, but with substantial functional limitations that are secondary to several manifestations of CHD, such as CHF, whose incidence has been increasing steadily, particularly in older populations, suggesting that we now face a real 'CHF epidemic'. The National Health and Nutrition Examination Survey (NHANES) epidemiological study reported that the prevalence of CHF is less than 5% among individuals aged 65 years or younger, but doubles among those older than 75 years,[2] and data from the World Health Organization (WHO) suggest that these figures differ little around the world, at least in more affluent countries.

As is discussed in this chapter, randomized clinical trials, and also meta-analyses and observational studies, have demonstrated that integrated cardiac rehabilitation (CR) programmes are highly effective in accelerating functional recovery and in improving exercise tolerance, adherence with secondary prevention measures, health-related quality of life (HRQOL) and also long-term prognosis after acute cardiac events.[3–6] As a result, the most recent guidelines clearly define the core components and outcome measures of CR and secondary prevention programmes and indicate CR as an integral component of long-term care of patients with CHD and CHF.[7,8]

Utilization of cardiac rehabilitation services: an international perspective

Despite this considerable amount of evidence and the fact that CR programmes are recommended (class I) by the European Society of Cardiology (ESC),[9] American Heart Association (AHA) and American College of Cardiology (ACC)[10] in the management of CHD and CHF,[11] prescription of CR programmes and diffusion of CR services are still relatively limited.

The level of CR service coverage across the European Union could be estimated from a survey of 454 phase 2 (medium-term recovery after hospital discharge) and 383 phase 3 (long-term maintenance) centres in 13 countries. Fewer than 50% of eligible patients participate in CR rehabilitation programmes in most European countries, with services in particularly short supply in countries with the greatest burden of cardiovascular diseases.[12] According to another survey of the European Society of Cardiology, only 67% of patients are prescribed CR soon after coronary artery bypass surgery, and this proportion drops to 49, 35 and 17% among those with recent myocardial infarction, coronary angioplasty or chronic myocardial ischaemia, respectively. Furthermore, utilization of CR services is widely variable cross-nationally, with an average participation after any type of CHD event ranging from 4% in Spain to 71% in Slovenia.[13] In the recently published results of the third EUROASPIRE Survey, the scenario is similar: less than 50% of CHD patients were advised to participate in a CR

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programme after hospitalization and about 75% of those advised attended at least half of the sessions; in summary, only about one-third of the originally eligible population.[14] More importantly, the data are limited to patients younger than 70 years who, in that survey, were selected for obtaining information on CR service coverage. Given the almost systematic exclusion of older patients that has been reported also by the most recent meta-analyses of CR in patients with CHD[15] or CHF,[16] under-prescription is expected to be even more marked in the older subset of the clinical population of cardiac patients.

Under-prescription of CR is similar in the USA, where only about 20% of appropriate candidates of any age, and about 10–15% of those older than 70 years, are estimated to participate in CR programmes, despite this treatment being acknowledged and recommended as a key component of secondary prevention programmes also in subjects older than 75 years.[17]

Cardiac rehabilitation: definition and aims

CR is defined as the 'sum of activities and interventions required to ensure the best possible physical, mental and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume their proper place in society and lead an active life'.[18]

In this perspective, CR and secondary prevention are aimed at (a) preventing the disability that may result from heart disease, particularly in older persons and in those with occupations implying physical exertion, and (b) preventing subsequent cardiovascular events. These goals can best be achieved through programmes combining the use of evidence-based prescription of drug therapy with exercise training and education, counselling, behavioural strategies and psychosocial interventions to help patients optimally control their coronary risk factors.[15] Therefore, CR is an integrated process of care, the aims of which are well beyond the simple functional assessment and prescription of exercise (Table 45.1), and which is currently indicated not only for cardiac patients already disabled or at increased risk of disability, but also for those with a diagnosis of CHD, intermittent claudication or with coronary risk factors. The benefits of CR programmes have been well documented in young and middle-aged CHD patients, whereas older patients rarely have been included in CR programmes and are poorly represented in clinical trials.[19,20] On the other hand, one randomized clinical trial did show that CR is at least as effective in older as in adult patients.[21] Despite such evidence, older patients are still less likely to be referred to formal CR programmes and, when referred but not encouraged enough to participate, in general experience a poor compliance with programmes. At least in part, the scant referral of older patients to CR programmes could be related to their more compromised clinical and functional status, due to frailty and greater burden of comorbidity resulting in disability.

Table 45.1 Aims and role of cardiac rehabilitation as an integrated secondary prevention tool.

- Clinical support to optimize pharmacological and non-pharmacological therapy
- Risk stratification, to define the probability of new events and deterioration of cardiac function, overall functional capacity and quality of life
- Assessment of physical exercise capacity, with exercise prescription in short-term training and long-term maintenance programmes
- Assessment of cardiovascular risk factors and implementation of counselling and education programmes to promote a healthy lifestyle
- Assessment of psychosocial and occupational profile, to design interventions aimed at promoting an active lifestyle
- Clinical and instrumental follow-up, to improve the efficacy of secondary prevention programmes

Although epidemiological data show that patients aged 75 years and older requiring cardiac care are increasing, only limited age-specific data are so far available from observational studies reporting CR in elderly individuals.[22] Most of these data refer to patients with an average age <75 years,[21,23,24] and from studies of post-infarction CR with small numbers over 75 years of age.[21] Nevertheless, several studies have demonstrated that, compared with adults, older patients derive from exercise-based CR similar, and sometimes greater, relative improvements in exercise tolerance and self-reported physical function. Suaya *et al*. recently demonstrated in a large cohort of older US Medicare beneficiaries, who had been hospitalized for CHD events or myocardial revascularization, that CR users had a better five-year survival.[25] After fully adjusting for a series of potential confounders, depending on the analytical procedure, mortality rates were from 21 to 34% lower in CR users than non-users: results similar to those observed in randomized controlled trials and meta-analyses in younger populations. Mortality reductions extended to all demographic and clinical subgroups, including patients with recent myocardial infarction, recent myocardial revascularization or CHF. Interestingly, the benefit was progressively greater with advancing age and reached the maximum at 85 years or more. Unfortunately, only 12% of initial total population was prescribed CR. CR users with 25 or more sessions were 19% less likely to die over 5 years than matched CR users with 24 or fewer sessions ($p<0.001$). The association of number of CR training sessions with outcome has recently been confirmed in another large cohort of older patients.[26]

The progressively shortened in-hospital stay after an acute myocardial infarction (from about 10 to only 4

days in the past 20 years)[27] reduces the risk of physical deconditioning, but also the time available to check physical activity and promote the lifestyle changes that are necessary to reduce cardiovascular risk; this reinforces the need for CR programmes that function as comprehensive, secondary prevention services and are based in-hospital, and also in the community or at home. Chow *et al*., recently have demonstrated that early lifestyle modifications (within 1 month after acute CHD events) strongly predict short-term prognosis, reducing the six-month risk of myocardial infarction/stroke/death.[28] For this reason, behavioural modification should be given priority similar to other preventive medications immediately after acute coronary syndromes.

Owing to better clinical management of cardiac diseases leading to improved survival rates, and to increasing evidence on the beneficial effects of CR in a wide range of cardiac conditions, the delivery of CR has changed remarkably over the past 30 years. In the 1960s, patients recovering from uncomplicated myocardial infarction accounted for almost the totality of referrals for CR. Complicated post-infarction patients or patients recovering from myocardial revascularization have also been enrolled in CR programmes in later years. Patients once considered at too high risk to participate in CR programmes, such as those with persisting myocardial ischaemia, CHF or harmful arrhythmias, are currently enrolled in CR programmes based on more gradual, protracted and, most often, supervised exercise training.[6,29,30] Furthermore, as a result of the progressive ageing of the population, CR should now be provided to increasing numbers of older patients, characterized by more complicated coronary illness, comorbidities,[6,31] functional or cognitive impairment, emotional disorders or social isolation, which all may concur to reduce the enrolment rate in, and adherence to, standardized CR programmes. Paradoxically, although some of these factors represent specific indications to CR, female gender, older age, a low formal education and, most importantly, functional impairment, are all negative predictors of enrolment in CR. Therefore, CR centres have to become familiar with the aims and skills of multidimensional geriatric assessment, to implement strongly individualized programmes that may promote the extension of CR to frail, older individuals.

Studies have proven that CR is at least equally effective in younger and older cardiac patients,[31] even those as old as 86 years,[32] to improve their exercise tolerance and HRQOL. However, no one study has yet demonstrated the efficacy of CR with respect to outcomes that are most typically desirable in geriatric medicine, such as reverting or limiting the progression of functional dependence in frail, older individuals.

Secondary prevention strategies in integrated cardiac rehabilitation programmes

Guidelines indicate that secondary prevention should be based on non-pharmacological and pharmacological interventions that can reduce the risk of new events and disease progression and should be aimed at improving both the prognosis and HRQOL. Non-pharmacological interventions consist of education, counselling and psychosocial interventions targeted at smoking cessation, improving dietary habits, controlling body weight and increasing physical activity and long-term adherence with prescriptions.

Educational principles

A meta-analysis of 37 trials[33] found that CR programmes including psychological and/or educational interventions resulted in a significant reduction in incident cardiovascular events at 1–10 years, with studies with the greatest response to intervention showing the greatest impact. The desirable characteristics of the educational and counselling approach have been outlined after a meta-analysis demonstrating that the most important determinant of effectiveness is the quality of intervention,[34] defined as behaviourally oriented interventions adhering to the five principles of adult learning:

- relevance (tailored to patients' knowledge, beliefs, circumstances)
- individualization (tailored to personal needs)
- feedback (informed regarding progress with learning or change)
- reinforcement (rewarded for progress)
- facilitation (provided with means to take action and/or reduce barriers).

Behavioural techniques such as self-monitoring and personal communication, including written or audiovisual techniques, may further improve the outcome, with information provision alone found to be less effective.

Psychosocial interventions

Some anxiety and depression are found in at least 20–25% of patients with various forms of heart disease but, particularly when they persist, should not be accepted as an appropriate reaction to heart disease. Emotional disorders reduce exercise capacity,[35] HRQOL and adherence to secondary prevention measures and substantially increase the risk of new events. Depressive disorders are probably more common among older patients, who frequently suffer from isolation and financial constraints, which are negative prognostic factors after myocardial infarction. However, the long-term consequences of emotional disorders among older cardiac patients in CR programmes have been poorly addressed, and patients 75 years of age and older are at

higher risk of under-recognition and under-treatment of depressive disorders.

Randomized trials proved that early psychological interventions improve the mood of middle-aged cardiac patients,[36] but information on efficacy at older ages is not available. However, particularly for most severe or disabling cases of persisting depression, psychological support therapies should be used in conjunction with antidepressants. Selective serotonin reuptake inhibitors, such as sertraline, which was proven to be safe and effective in a randomized trial enrolling patients depressed after an acute coronary syndrome, are probably the agents to be preferred.

Smoking cessation

A Cochrane review confirmed the beneficial effects of smoking cessation, which reduces the risk of new events by up to 40%,[37] similarly to what is seen with pharmacological correction of other cardiovascular risk factors. Smoking induces chronic dependence that makes relapses highly probable. Systematic encouragement of smoking cessation is based on the '5A-strategy' of Asking, Assessing, Advising, Assisting, Arranging. In this process, it is necessary to identify smokers, to evaluate the degree of their dependence and their willingness to quit, to support those who are trying to quit with behavioural counselling, prescription of nicotine substitutes and participation in educational meetings, with regular follow-up visits.

Healthy eating and diet

Dietary prescriptions, adapted to local habits and individualized as much as possible, should be aimed at controlling body weight and provision of all elements of proven efficacy in secondary prevention. Dietary habits should be assessed objectively, with the use of reproducible questionnaires and checking individual knowledge of nutrients and of possible substitutes. Education, rather than prescription, should be provided, limiting dietary restrictions to patients with defined metabolic abnormalities. Education and counselling should be provided by professional dieticians, who perform better than physicians in obtaining a long-term reduction in plasma cholesterol levels.

Increasing physical activity

Promoting a long-term increase in usual physical activity is a fundamental objective of integrated CR programmes finalized at secondary prevention. Regular physical exercise improves the lipid profile and delays the progression of CHD in middle-aged, male patients and reduces cardiovascular mortality in the general population. In the Harvard Alumni Health Study,[38] the relative (i.e. perceived) intensity of physical activity was a strong predictor of lower CHD rates, with a clear dose–effect relationship and an effect that was similar, if not superior, among subjects older compared with those younger than 70 years. Interestingly, the absolute intensity of physical activity did not perform as well as the relative intensity in distinguishing CHD risk groups, suggesting that physical activity recommendations need to be individually tailored. Standard recommendations of regular performance of activities at an intensity of at least 3 METs (Metabolic Equivalents, 1 MET corresponding to 3.5 ml of oxygen consumption per kilogram of body weight; see also below) may therefore be inappropriate, especially for older persons.[38]

Long-term adherence and follow-up

Once the process of short-term recovery is complete, the emphasis of CR shifts to long-term maintenance of physical activity, lifestyle changes and prophylactic drug therapy, in the perspective of 'comprehensive cardiac care' as the final goal, following evidence-based recommendations.

A systematic review of 12 randomized trials of secondary prevention programmes in CHD found that structured disease management programmes improve risk factor profiles and secondary preventive treatment, while reducing hospital readmissions and enhancing HRQOL.[39] The programmes included in the review differed considerably: all were multifaceted, with about half including medical and lifestyle treatments, and the rest were predominantly lifestyle and psychosocial interventions. Most were hospital based, but two conducted in UK primary care suggested that a structured approach benefits HRQOL and uptake of secondary prevention. Indeed, long-term adherence with recommendations and prescriptions made during CR is difficult to maintain, usually being reduced to 50–60% at 1 year and to 20–30% at 3 years. Therefore, to enhance long-term maintenance of the goals attained during CR, it is highly recommended that structured care and follow-up are provided in primary care and studies suggest that low-cost, physical training programmes carried out in the community are safe and help patients maintain the physical performance levels they had attained during hospital-based rehabilitation. The GOSPEL study, the results of which have recently been published, is the first trial to demonstrate that a multifactorial, continuously reinforced intervention up to 3 years after post-infarction CR is effective in decreasing the risk of several adverse outcomes, although statistical significance was reached for non-fatal reinfarction only.[7]

The structure of cardiac rehabilitation programmes

CR programmes usually consist of three phases, each representing a different step in the progression of individual patient care: in-hospital care, the early post-discharge and exercise training period and long-term follow-up. Common to each phase and irrespective of which model of CR is chosen, is the need for individually tailored interventions.

Phase I occurs during in-hospital stay, when a 'step change' (any acute coronary event, cardiac surgery or first diagnosis of heart failure) has occurred in a patient's cardiac condition. Medical evaluation and treatment, reassurance and information aimed at reducing emotional distress, risk factor assessment, mobilization and discharge planning are the key elements during this phase.

Phase II includes the early post-discharge period – when baseline assessment and initial counselling on self-management of heart conditions usually take place – and subsequent structured exercise programmes, which are carried out either in a hospital setting or in outpatient clinics or, at least for selected patients, at home.[32] Guidelines[29] suggest that, for greatest secondary prevention success, training must be associated with educational and psychological support and advice on risk factors, such as smoking cessation and weight management, vocational rehabilitation to assist return to work or retirement and referral to a psychologist, cardiologist or exercise physiologist. It has been demonstrated that phase II programmes of integrated, multicomponent CR can be undertaken safely and successfully also in the community.

Phase III involves the long-term maintenance of physical activity and lifestyle changes. Available evidence suggests that both must be sustained for benefits to continue. Membership of a local cardiac support group, which involves exercise in a community centre such as a gymnasium or leisure centre and structured care and follow-up in primary care, may help maintain physical activity and behavioural change.

Baseline assessment

Baseline evaluation is a process of crucial importance that has to be completed prior to enrolment in a cardiac rehabilitation programme. In this process, several clinical, functional and, particularly in older persons, emotional, cognitive and social elements must be taken into account, as they are used to assign the patient to the programme most appropriate for their clinical and functional conditions, to pursue reliable and clinically valuable outcomes, to reduce the probability of programme-related complications and to promote individual adherence to the programme. Exercise training programmes for older persons also need to take into account commonly associated comorbidities that can alter the modalities and intensities of the exercise that is required to produce a training effect. These include, but are not limited to, CHF, arthritis and osteoporosis, chronic lung disease, diabetes and peripheral or cerebrovascular disease.

Risk stratification

Risk stratification and assessment of exercise capacity are the two fundamental steps of baseline evaluation. These two steps are closely linked, as information gathered with assessment of exercise capacity is used not only for an appropriate exercise prescription to each individual patient, but also as one of the criteria for assigning each patient to one risk category. Risk stratification will serve, on the other hand, to optimize pharmacological therapy and possibly to indicate the need for invasive procedures (e.g. coronary angiography and myocardial revascularization; implantation of pacemakers or intracardiac defibrillators), but also as further information to be taken into account for exercise prescription.

In essence, risk stratification relies upon the evaluation of clinical stability, left ventricular function, presence of residual myocardial ischaemia or of sustained ventricular arrhythmias and exercise tolerance. Following the criteria outlined in Table 45.2, patients are classified as at low, intermediate or high risk.

Assessment of exercise capacity

Baseline exercise capacity can be evaluated by several methods, among which the most commonly used are the ergometric stress test, the cardiopulmonary exercise test and the six-minute walk test. Each of them is indicated in different conditions and provides different information.

The *ergometric stress test* is one of the most important diagnostic and prognostic instruments in cardiac patients, with the objectives of determining (a) the exercise capacity, which is used for defining baseline functional capacity, training prescription and evaluation of training results, and (b) the coronary reserve and the inotropic reserve. The cycle ergometer and the treadmill are the most common equipment for exercise stress testing, using protocols that may differ for the type of workload (constant versus increasing), the modality of delivering the workload (continuous versus at intervals), the rate of increase in workload (high versus low) and the type and level of endpoint (predetermined versus symptom-limited, sub-maximum versus maximum). The specificity of the test is reduced with increasing age and its sensitivity, which should theoretically increase with increased prevalence of CHD, may also be reduced. Indeed, it has been reported that a maximum, or symptom-limited, exercise stress test is possible in only about 50% of individuals older than 75 years of age, as a consequence of ageing-associated reduction in exercise capacity, detraining and increased prevalence of comorbidities which may limit exercise capacity. Furthermore, the current use of a predetermined (220 – age), maximum theoretical heart rate to assess the maximum intensity of physical exercise does not represent a robust reference method, particularly in older patients with intrinsic functional limitations. The type of equipment and the protocol should be chosen on an individual basis, in order to adapt to the expected, individual exercise tolerance. The test duration should not exceed 10–12 min and smaller increases in workload (e.g. 10 W per step) are recommended for

Table 45.2 Criteria for baseline risk stratification of candidates to a cardiac rehabilitation programme.

Criterion[a]	Class of risk[a]		
	Low	Intermediate[b]	High[b]
Clinical course	Uncomplicated In-hospital course	Uncomplicated In-hospital course	• Severe complications (e.g. cardiac arrest; shock; cardiac/respiratory failure) during in-hospital course, OR • Persisting clinical instability (e.g. cardiac failure; renal failure)
LVEF (%)	≥50	31–49	≤30
Myocardial ischaemia	NO	YES	YES
		• At intermediate (≥100 W) workload, OR • With ST-segment depression <2 mm, OR • Limited asynergies or perfusion defects on stress echocardiography or scintigraphy	• At low (<100 W) workload, OR • With ST-segment depression >2 mm, OR • Extensive asynergies or perfusion defects on stress echocardiography or scintigraphy
Ventricular arrhythmias	NO	NO	YES Sustained ventricular arrhythmias
Exercise capacity	≥6 METs	<6 METs	<4 METs

[a]LVEF, left ventricular ejection fraction; METs, metabolic equivalents.
[b]Presence of any condition listed causes patient assignment to that risk class.

patients with expectedly reduced functional capacity. The indications and contraindications and the diagnostic criteria for exercise stress testing are detailed in guidelines of the American College of Cardiology/American Heart Association.

The *cardiopulmonary exercise test* is an ergometric test with simultaneous measurement of oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory quotient (VCO_2/VO_2) and pulmonary ventilation. This requires relatively expensive equipment, which needs frequent calibration. Most commonly, the workload is increased by 10 W every 1–2 min. The large variability in measurement of VO_2 – which is influenced by age, gender, level of fitness, severity of disease and comorbidity – is the main limitation to standardizing this test. Nonetheless, $VO_{2\,max}$ is the best available objective measure of aerobic capacity, although cardiac patients only rarely can exercise up to an intensity corresponding to their $VO_{2\,max}$. Therefore, the VO_2 at peak exercise indexed by body weight ($VO_{2\,peak}$, $ml\,min^{-1}\,kg^{-1}$) is a more frequently used measure of exercise tolerance. During exercise, the respiratory quotient increases progressively until it becomes >1, which corresponds to the anaerobic threshold (AT), a useful indicator of the workload that an individual can tolerate without overproducing lactic acid. Unfortunately, it cannot always be identified, particularly in patients with markedly reduced exercise tolerance ($VO_{2\,peak}$ $<10\,ml\,min^{-1}\,kg^{-1}$). This test is particularly indicated to measure exercise tolerance and to define the prognosis of patients with CHF, and $VO_{2\,peak}$ or AT is also used to make the decision on patient inclusion in the waiting list for heart transplant.

With the *six-minute walk test*,[40] exercise tolerance is assessed by measuring the distance that a patient can walk at her/his fastest possible pace in 6 min. A stopwatch, a notepad and a measuring tape are the only materials required. The test has been standardized for application in a linear, enclosed, quiet and seldom travelled corridor, at least 30 m in length, which must be marked throughout its length, to determine the walked distance accurately. Two chairs positioned at the two extremities of the corridor further delimit the path and allow the patient to sit if they become so symptomatic during the test as to need some rest.[40] For safety purposes, the test is best carried out with continuous, telemetric control of heart rate and rhythm and peripheral oxygen saturation, and in association with use of scales aimed at quantifying the perception of fatigue; emergency equipment must be on hand. The main strengths of this test are that it is easy to carry out, does not require any special equipment and is based on a 'natural' activity of common daily life. For these characteristics, the test has been extensively used to evaluate exercise tolerance, especially in CHF and in older

post-infarction or post-surgery patients, particularly when they are disabled to such an extent that they cannot perform reliably in a conventional ergometric stress test. The main limitation, on the other hand, is the low reproducibility, which is essentially due to variable motivation and self-assessment of fatigue and which is improved with the use of standardized encouragement by the test monitor.

The physical exercise training programme

Physical exercise training is the core component of CR programmes, essentially aimed at improving exercise tolerance and, through this goal, at reducing disability, improving quality of life and control of cardiovascular risk factors, thereby reducing long-term morbidity and mortality.

Efficacy and safety are the most important characteristics to be considered in prescribing the physical exercise training in a CR programme. Physical training is effective when it produces measurable benefits at the cardiocirculatory and skeletal muscle level and is safe when it is not associated with either short- or long-term harmful effects.

Baseline assessment data are used to design individually adapted, effective and safe training programmes. To this purpose, all factors that may limit the capability of exercising (e.g. presence and severity of angina or of concurrent diseases, such as disabling osteoarthritis) and the response to the baseline, symptom-limited exercise stress test to be used to calculate the individual training workload, are the elements to be taken into fundamental account. The energy expenditure during physical exercise is influenced by the type of exercise (e.g. isotonic versus isometric), the amount of skeletal muscles involved, aerobic capacity and also by the intensity, duration, frequency and modality of exercise sessions.

Intensity of exercise training sessions

Setting the intensity of exercise is a process of crucial importance, based on individual data and ideally leading to the prescribing of training at an intensity which is adequate for each patient. The intensity of exercise can be measured directly – as the amount of mechanical work produced ($kg\,min^{-1}$; $W\,min^{-1}$; $J\,min^{-1}$) – or indirectly – from measures of energy expenditure (such as kilocalories or METs) or from exercise-related changes in physiological variables (such as heart rate or VO_2). The method based on changes in heart rate is the simplest and the most commonly used in the clinical practice. Following this approach, a training exercise programme is prescribed at an intensity (i.e. load) that produces an increase in heart rate (defined as the 'target' heart rate) to 70–85% of the maximum heart rate that the patient has attained during a symptom-limited, baseline exercise stress test. The beneficial effects of training are maximized, exercise-related complications and lactic acid production in the peripheral organs are minimized and the onset of fatigue is delayed, by maintaining the heart rate within its target range. Alternatively, training is prescribed at an intensity that will produce an increase in VO_2 to 60–80% of the $VO_{2\ peak}$ that the patient has attained at baseline.

To reduce further the risk of complications, it is recommended that the intensity of exercise is increased gradually, allowing a few minutes of warm-up before reaching the training workload. Beyond a generic recommendation of starting a training programme at lower intensities with gradual increments during the following weeks, no conclusive data are available on how adapt the training intensity to an individual patient's clinical and functional profile. For practical purposes, however, it can be suggested that patients with CHD but without inducible myocardial ischaemia or left ventricular systolic dysfunction start their training at an intensity corresponding to 70–85% of maximum heart rate, those with inducible ischaemia exercise at an intensity almost corresponding to the ischaemic threshold, whereas those with systolic left ventricular dysfunction or overt CHF should exercise at lower intensities, that is at 70–80 and 60–70% of maximum heart rate, respectively.

In addition to aerobic exercise, strength exercise is also increasingly being recognized as a useful component of the training programme for selected patients and muscular strength and endurance improve with strength training of moderate intensity in low-risk patients, even at older ages. Information on safety and usefulness of strength training in high-risk patients is still limited, although it has been suggested that low-intensity weight training can be safely and effectively introduced in the circuit training programme for patients with CHD – even in the presence of inducible ischaemia or left ventricular systolic dysfunction – or for patients with CHF.

Duration of exercise training sessions

An individually prescribed duration of exercise sessions may range from 5 to 60 min, being indirectly proportional to the intensity of exercise. The duration of each session is usually shorter in the initial phase of training, to be increased gradually thereafter. An excessively prolonged duration may be associated with increased risk of lactoacidosis and orthopaedic complications. However, a reasonably prolonged exercise is necessary to activate the energy metabolism pathways: it is acknowledged that, for an intensity at about 80% of maximum heart rate, the optimum duration is between 20 and 30 min. A practical method for determining the most appropriate duration of sessions is to use the product of workload and duration of exercise to calculate the energy expenditure, which should be about 250–300 kcal per session or 1000–1500 kcal per week.

Frequency of exercise training sessions

In the initial phase of an exercise programme, when the exercise intensity is gradually increased, daily sessions, on at least 5 days per week, are to be preferred, also to check most accurately the cardiovascular response to exercise. This is particularly important because, during the initial phase of training, exercise-related changes in heart rate and arterial pressure may be substantially different from those observed during the baseline stress test. Following the initial phase, three sessions per week are usually adequate to maintain the training effect. It should be remembered that, if the training programme is interrupted, exercise capacity usually is reduced by 50% within 4–5 weeks.

Modality of exercise training sessions

A training programme can be set up following the continuous, the interval and the circuit training modalities. The continuous training modality, which is particularly effective in increasing cardiovascular and muscular endurance capacities, is carried out at moderate intensities, with a prolonged duration and without periods of recovery. In the interval training modality, periods of exercise at higher intensity are alternated with periods of recovery or of exercise at lower intensity. The circuit training programme is based on a series of different exercises (with or without equipment) carried out in a sequence. Circuit training is a programme of moderate intensity which improves not only the endurance capacity and muscular strength, but also neuromuscular coordination and agility. Despite these multiple positive effects, this training modality is still rarely used in CR. Various equipment (e.g. cycle ergometer or treadmill) and various types of calisthenics have been used in training programmes mostly aimed at enhancing aerobic capacity.

The training is the main phase of the programme, aimed at improving the delivery of oxygen to the working muscles through both enhanced oxygen transportation capacity and extraction and at maximizing caloric expenditure. Continuous and rhythmic exercises involving large muscle groups, such as walking, stepping on a staircase and exercising on a cycle ergometer, are the most effective modalities of aerobic training. Calisthenics, particularly those involving large muscle masses, and also strength training and recreational activities, can also be usefully included.

A 5–10 min cool-down phase at a lower workload should follow the training phase, for a gradual recovery of heart rate and arterial pressure to their baseline levels. A too brisk interruption of exercise can produce arterial hypotension and syncope, especially in older persons with blunted cardiovascular reflexes.

Progression and duration of training programmes

During the course of a training programme, the exercise intensity should be adapted to the patient's improved exercise capacity. Change in heart rate at sub-maximum exercise is the simplest method to be followed for this purpose. However, particularly in older patients and in those treated with beta-blocking agents, these may prove to be unreliable indicators of an improved aerobic capacity. Therefore, use of the Borg's scale, which assesses the rate of perceived exertion (RPE),[41] is a commonly recommended, simple method to confirm additionally that exercise tolerance has improved from baseline. With a maximum possible value of 20 on the scale, patients should exercise at an RPE of 13–15. A reduction in RPE can be the consequence of enhanced cardiovascular and muscular fitness, but also of improved emotional profile and of increased confidence with the schemes of exercises and use of equipment. In any case, when the RPE at sub-maximum workloads is reduced, the intensity of exercise can be safely increased, in order to obtain a further training effect. Assessment of RPE is of particular importance in frail, older patients with CHF or comorbidity or after prolonged bed rest for complicated cardiac surgery. In these subgroups, a standardized and reproducible assessment of perceived fatigue should guide the progression through strictly individualized rehabilitative programmes, initially setting the exercise intensity at an RPE of 9–11, which corresponds to about 60% of maximum heart rate and slowly progressing to an RPE of 12–13 over the following weeks.

The duration of training programmes is one of the most difficult characteristics to be exactly defined. Ideally, a training programme should be prolonged enough to induce positive changes in functional conditions. However, this objective has to confront the organizational constraints of rehabilitation centres, which have to offer access to new patients following turnover programmes. Furthermore, exact information on the relationship between programme duration and attainable outcomes is still lacking, with the exception of documentation on variable increments in non-standardized measures of exercise tolerance reported by training programmes of variable duration. A period of 3–12 weeks is generally recommendable, with longer durations needed for patients at higher risk. At least three sessions per week at high workloads for 4 weeks are the minimum prescription to obtain a measurable and clinically valuable effect, and more sessions are necessary when – for safety reasons when faced with a markedly deteriorated functional profile or unstable clinical conditions – the workload has to be set initially at a low level. Following these general considerations, a programme duration of at least 3 weeks is sufficient for most low-risk patients after uncomplicated infarction or cardiac surgery, whereas for patients at higher risk or with CHF a duration of 4–6 and 8–10 weeks, respectively, is deemed to be more appropriate. The programme duration should be prolonged also for older patients, who are usually trained at lower initial intensities. It should be remembered that the duration of the training programme

is also a function of many other clinical elements, such as the adaptive changes in heart rate and arterial pressure, the absence of symptoms, the RPE, the capacity of obtaining at least a 10–20% increase in exercise tolerance from baseline, the stability of the emotional profile and adherence to the structure of overall preventive programme.

As already mentioned, long-term, community-based physical exercise maintenance programmes are effective in preserving the otherwise declining improvement in exercise tolerance attained with participation in hospital-based rehabilitation programmes.

Safety of training programmes

Patients are admitted to a training programme when in a stable clinical condition and in the absence of absolute contraindications to physical exercise (Table 45.3).

The safety of physical training in CHD patients has long been a source of considerable controversy. Studies in the 1970s–1980s reported an incidence of non-fatal events ranging from 1 event per 34 000 h of exercise-patient to 28 events per 2 350 000 h of exercise-patient, with an incidence of fatal events ranging from 1 event per 116 000 to 1 event per 2 350 000 h of exercise-patient. Lower overall rates and absence of any fatality have been reported in two reviews[42,43] that were based on more recent studies. Whether continuous ECG monitoring may reduce the risk of complications is still unknown. Usually, high-risk patients are constantly monitored during the whole training programme, whereas low-risk patients are monitoring only during the first few sessions. However, studies have suggested that the overall incidence of complications is low and similar across risk categories and that the few complications are represented mostly by 'minor' events such as angina, ST-segment depression or non-sustained cardiac arrhythmias. For the purpose of safety, multiple parameters must be taken under control during exercise training, in particular the linearity of the increase in heart rate and arterial blood pressure, ECG morphology and the RPE. Surveillance and monitoring must be especially close during the initial phase of the programme, when physical detraining or difficulties in learning how to carry out exercises may contribute to abnormal increases in heart rate or arterial pressure. Adapting exercise prescriptions to a limited functional capacity – particularly in older, disabled and comorbid individuals – further contributes to the feasibility and safety of exercise programmes. A skilled staff that includes several different professionals, such as physical therapists, nurses and technicians, and on-site devices and drugs that are necessary for immediate treatment of emergencies are the final elements that support programme safety.

Table 45.3 Contraindications to exercise training.

Absolute	• Acute myocardial infarction • Unstable angina • Uncontrolled ventricular cardiac arrhythmias • Severe aortic stenosis • Unstable heart failure • Pulmonary embolism or infarction • Myocarditis or pericarditis • Aortic dissection
Relative	• Uncontrolled arterial hypertension (SAP/DAP >180/110 mmHg) • Tachy- or bradyarrhythmias • High degree atrioventricular block • Electrolyte abnormalities • Hypertrophic cardiomyopathy • Mental or physical impairment leading to inability to exercise adequately

Exercise training programmes in special cardiac conditions

Cardiac surgery

Exercise training after cardiac surgery can start when the clinical conditions have become stable and it is usually preceded by short programmes of respiratory physical therapy to recover respiratory dynamics and of low-intensity exercise to improve mobility and flexibility. Extensive neurological and cognitive evaluation is particularly recommended in older persons, in whom cerebral complications of prolonged anaesthesia and extracorporeal circulation are more likely to occur. In these patients, an early rehabilitation programme is aimed mainly at improving mobility and independence in activities of daily living. In the absence of specific contraindications that may occur after surgery (e.g. anaemia with Hb $<10\,g\,dl^{-1}$; pleural or pericardial effusion; delayed or complicated healing of surgical wounds), a six-minute walk test is prescribed as soon as the patient is able to walk independently (on average, 10 days after surgery). A baseline, symptom-limited ergometric stress test is carried out 3–4 weeks after surgery, when the sternum has usually stabilized and thoracic pain has relieved. As previously described, data acquired during the stress test are used to select the appropriate intensity for exercise training, which low-risk patients can usually be taught to self-manage at home without risk. As for other categories of cardiac patients, assessment of cardiovascular risk factors, associated with education, counselling and behavioural strategies to help achieve the best optimal control of coronary risk factors, is an essential component of medium- and long-term rehabilitation programmes.

Chronic heart failure

CHF patients must be clinically stable while on optimized drug therapy for at least 1 month before their exercise

capacity can be assessed for potential enrolment in a physical training programme. Particularly in the presence of permanent atrial fibrillation, the cardiopulmonary exercise test is the preferred method for assessment,[30] as it can evaluate aerobic capacity and, hence, exercise capacity also when the heart rate response to exercise is inappropriate or difficult to determine precisely. Endurance training with a cycle ergometer, with the intensity set at 50% of the maximum workload attained in a baseline cardiopulmonary exercise test, 15 min sessions of interval training (exercise for 30 s, followed by 60 s of recovery or very light work), is the most commonly adopted training modality for CHF patients, since it would induce the best possible training effect without excessively increased fatigue or undesirable metabolic effects. Alternative protocols include arm exercises, walking on treadmill, flexibility and respiratory exercises. More recently, studies have demonstrated some positive effects from association of endurance with strength training.[44] Since functional assessment of and exercise prescription to CHF patients require particularly high skills, these patients should participate only in programmes that are run by well experienced rehabilitation centres. At least in the initial phase, the training programme should be carefully supervised. Studies have demonstrated the feasibility, safety and efficacy of home-based, low-intensity training programmes for CHF patients but, again, no specific data are yet available for older individuals.

The physiological effects of aerobic training

Effects of aerobic training in middle-aged and older adults with coronary heart disease

The beneficial physiological effects physical training, namely improved exercise tolerance associated with less fatigue, less angina and increased sense of wellbeing, derive from both peripheral (vascular or skeletal muscle) and central (myocardial) adaptations.

Peripheral adaptations are mainly the consequence of improved skeletal muscle efficiency, leading to improved ability to extract oxygen from entering the blood supply and increased arteriovenous difference during physical exercise. This reduces the need for increasing cardiac output and, hence, the work that the heart has to do to bring an adequate amount of oxygen to the tissues at submaximum exercise. Central adaptations include increases in cardiac dimensions, stroke volume, cardiac output and indexes of left ventricular function,[45,46] which have been reported after training programmes of variable duration in middle-aged patients with CHD. The mechanisms of physiological adaptations to exercise training in older patients may be somewhat different from those seen in middle-aged patients. Probably because of the ageing-associated increase in myocardial and vascular stiffness, adaptability to central remodelling is reduced and exercise-induced adaptations in older coronary patients appear to be almost exclusively localized at the periphery. After 3 months of aerobic training, peak exercise cardiac output, peripheral vascular conductance and hyperaemic calf blood flow were unchanged in older, low-risk patients with CHD, despite the fact that their exercise tolerance, $VO_{2\,max}$ and arteriovenous oxygen difference have increased.[47] Histological analysis of skeletal muscle biopsies showed a marked increase in capillary density and in oxidative enzyme capacity that fully account for improved adaptation to exercise.[47]

Effects of aerobic training in patients with chronic heart failure

Reduced exercise tolerance with increased breathlessness and muscle fatigue are the symptomatic hallmarks in CHF patients, who limit their activity to avoid these symptoms. This may result in further detraining, possibly leading to a vicious circle of progressively reduced exercise tolerance.

The origin of these symptoms is multifactorial, involving central cardiac factors (left ventricular systolic and diastolic dysfunction with increased pulmonary capillary pressure), central pulmonary factors (impaired ventilatory mechanics and increased physiological dead space; altered ventilation/perfusion ratio; hypoxia of ventilatory muscles) and peripheral circulatory and muscular factors (impaired vasodilatation during physical exercise; metabolic and structural alterations of skeletal muscles). Peripheral pathophysiological changes appear to be the most important determinants of exercise capacity in CHF, as systemic and pulmonary haemodynamics correlate poorly with exercise capacity or exertional breathlessness and, while central haemodynamics improve rapidly with drug therapy, improvement in exercise capacity may be delayed for weeks or months.

Skeletal muscle hypoperfusion has been observed in CHF both at rest and during exercise. This is directly related to CHF severity, is the consequence – together with sympathetic overactivity and parasympathetic withdrawal – of increased activity of endothelial ACE and reduced endothelial production of nitric oxide and is responsible for early occurrence of lactacidosis, which, in turn, produces muscular exhaustion and increases the ventilatory needs. It has also been demonstrated that unmyelinated and small myelinated afferents in muscle that are sensitive to metabolic changes related to work ('ergoreceptors') are responsible for the early circulatory response to exercise, including activation of the sympathetic vasoconstrictor drive, and that this reflex is exaggerated in CHF, probably because of sensitization by muscular acidosis during exercise. Limited physical activity, anorexia and increased circulating

substances with known catabolic effect, all contribute to inducing a certain degree of muscular atrophy, which correlates with the reduction in strength and exercise tolerance. However, functional data suggest that muscular atrophy cannot fully account for the reduced exercise tolerance. When strength is measured per unit of muscular area, it correlates poorly with $VO_{2\,max}$ and exercise tolerance. This is consistent with qualitative alterations of muscular fibres, represented by a reduction in slow-reacting, type I fibres – responsible for muscular endurance, with prevalent oxidative metabolism – with a relative increase in fast-reacting type II fibres, whose metabolic pathways rely mainly on glycolysis.

Randomized trials have demonstrated that physical training determines a sustained improvement in functional class, maximum ventilation, exercise capacity[48] and QOL in CHF patients, particularly when enrolled in long-term maintenance programmes. Although some improvement in left ventricular ejection fraction at rest and in maximum stroke volume during exercise has occasionally been described,[48] changes in central haemodynamics after training are generally modest. Thus, also in the case of CHF, the major adaptations to training appear to be peripheral. Many of the peripheral vascular and muscular dysfunctions that concur to reduce exercise tolerance in CHF are fully reverted, or at least partially corrected, by training. In particular, the endothelial production of nitric oxide in response to exercise is remarkably enhanced and the exaggerated ergoreflex activity is attenuated, with both effects contributing to reducing the inappropriately increased peripheral vascular resistance. Exercise training also reduces the concentrations of circulating norepinephrine and atrial natriuretic peptide. Analysis of percutaneous muscular biopsies, coupled with measurement of $VO_{2\,max}$ during a symptom-limited cardiopulmonary exercise test, suggests that structural and functional changes in skeletal muscles are a further determinant of improvement in exercise tolerance observed with training in CHF. Indeed, ultrastructural morphometry demonstrated a training-associated increase in skeletal muscle cell mitochondria, suggesting that the improved functional capacity is linked to an increased oxidative capacity of skeletal muscles and a concomitant reshift to type I fibres.

Evidence-based results of cardiac rehabilitation in different cardiac conditions

Coronary heart disease

Most randomized trials of CR in CHD have included mixed populations of patients with recent myocardial infarction, myocardial revascularization or angina and are based on exercise-only or exercise in addition to psychological and educational interventions, which is usually termed comprehensive CR.

The most recent meta-analysis included 48 trials and 8940 patients.[15] Compared with usual care, CR was associated with a significant 20 and 26% reduction in all-cause and cardiac mortality, respectively, and with larger reductions in plasma lipids, systolic blood pressure and rates of persistent smoking cessation. Rates of non-fatal myocardial infarction and revascularization and changes in high- and low-density lipoprotein cholesterol levels, diastolic pressure or HRQOL were similar with CR and usual care. The effect of CR on total mortality was independent of CHD diagnosis, programme of exercise intervention, length of follow-up, trial quality and trial publication date. In contrast to previous reports of greater benefit with comprehensive rehabilitation than with exercise-only programmes, the benefits were independent of type of rehabilitation programme. The authors suggested[15] that this may be because the follow-up in most studies was too short to observe indirect effects, which may need a longer time to occur. However, there are two alternative explanations. One is that exercise-only CR is likely to include psychological and educational support, even though not offered in a structured manner. The other is that most of the exercise-only trials were conducted in the pre-thrombolytic era, whereas most of the comprehensive trials were more recent. This means that the benefits in the comprehensive rehabilitation trials are likely to be additional to the already great benefit of thrombolysis, prophylactic medication and/or coronary revascularization. Only one trial included in the meta-analysis deliberately enrolled significant numbers of patients older than 75 years of age. In particular, this was the first randomized controlled trial demonstrating the feasibility, safety and efficacy with respect to exercise tolerance and HRQOL of rehabilitation in post-myocardial infarction patients as old as 86 years of age.[32] The uniqueness of this trial is confirmed by the fact that the ages of patients enrolled in other trials ranged from 48 to 71 years and, accordingly, recommendations for further trials including subsets of older patients were made in Taylor *et al*.'s review.[15]

The precise mechanism(s) by which physical exercise training reduces mortality in CHD patients is still to be completely elucidated. Exercise training exerts direct beneficial effects on myocardial oxygen demand, development of coronary collateral vessels and coronary endothelial function, cardiocirculatory autonomic tone, coagulation and clotting factors and inflammatory markers. However, reduction in mortality may also be mediated via the indirect effects of exercise through improvements in the risk factors for atherosclerotic disease.

Cardiac surgery

Although almost two out of three enrollees in CR programmes in Europe are recovering from cardiac surgery, only a few studies have specifically addressed the efficacy of CR after surgery. Furthermore, most meta-analyses have not examined the results of post-surgery CR separately from those in other clinical subsets. These aggregated analyses have demonstrated that CR is associated with a significant reduction in long-term mortality.

Information on the efficacy of post-surgery rehabilitation in older patients is even more limited, despite the demonstration that older age, together with female gender and comorbidity, are independent risk factors for cognitive, neurological and functional complications, prolonged hospital stay, worse long-term prognosis and early hospital readmission after cardiac surgery, which are all elements that would recommend greater participation of older surgical patients in rehabilitation programmes. Nonetheless, a recent review[49] demonstrated that in addition to age, disability, lower formal education, cardiac dysfunction and poor quality of life are all predictors of non-participation in rehabilitation after coronary artery bypass operations, although patients with these conditions would benefit the most from integrated, multicomponent CR programmes.

Chronic heart failure

After the success with newer pharmacological agents such as ACE inhibitors, beta-blockers and anti-aldosteronic agents, a further 'therapeutic revolution' has occurred recently in the management of CHF, consisting of a profound change in recommendations about physical activity. From the previous orientation in favour of restrictions on physical activity, the newest guidelines recommend therapeutic exercise programmes for the current management of CHF.[11] This came after the demonstration that supervised exercise training improves the functional capacity and quality of life of CHF patients, without any risk of unfavourable clinical events or deteriorating cardiac function, but rather with an anti-remodelling effect.

A review pooled the results of 81 studies of exercise training in CHF,[16] which differed considerably in the intensity (from 40 to 90% of $VO_{2\,max}$), the frequency (from one to seven per week) and duration (from 15 to 120 min) of exercise training sessions and in the overall programme duration (from 2 to 104 weeks). Despite these differences and the different characteristics of patients enrolled, a relatively homogeneous and significant improvement in exercise tolerance was reported in all studies. Pooled analysis has also demonstrated the absence of relevant, exercise-related adverse events and significant, positive effects of training on combined endpoints (all-cause mortality plus new events). A meta-analysis[50] including nine randomized trials with 809 patients (395 exercise training versus 406 controls) determined the effect of exercise training programmes of at least 8 weeks with follow-up data for at least 3 months on survival in patients with CHF due to left ventricular systolic dysfunction. Exercise training significantly reduced all-cause mortality and the combined endpoint of hospital readmission by 35 and 28%, respectively, with no statistically significant subgroup treatment-specific effect. Age comparison was limited to patients younger and older than 60 years, since most of those enrolled in randomized trials were younger than 65 years. Moreover, most patients enrolled in randomized trials were highly selected individuals with little or no comorbidity, unlike older cardiac patients seen in everyday clinical practice, and the surrogate endpoints that have frequently been adopted in those trials (e.g. changes in $VO_{2\,max}$) do not provide evidence that such therapy affects outcomes that are especially valuable in older persons, such as functional capacity or quality of life. Several controversies still need to be addressed. Exercise training is recommended for NYHA functional class II or III patients, tailored to the individual's exercise tolerance, because it improves exercise capacity and quality of life. However, ExTraMATCH[50] and the HF-ACTION trial[51] have provided somewhat contradictory results about its effectiveness on morbidity and mortality in stable patients. Limited information about combined aerobic, strength, interval, resistance and respiratory exercise training is available. Although the safety of all of these exercise modalities is undisputed, the question of the most effective training mode remains to be answered.

Key points

- Cardiac rehabilitation is an integral component of secondary prevention and is indicated for patients with a wide variety of cardiac conditions, ranging from coronary artery disease to chronic heart failure.
- The best results are obtained with integrated, multicomponent cardiac rehabilitation programmes, which include exercise training together with counselling and psychosocial measures that may help patients maintain sustained changes towards a healthier lifestyle. Studies suggest also that long-term maintenance programmes carried out in the community after the in-hospital phase may achieve better long-term results.
- Robust evidence from randomized controlled trials and meta-analyses supports the efficacy of cardiac rehabilitation on clinically relevant outcomes such as reduced long-term morbidity and mortality, enhanced functional profile and improved

control of cardiovascular risk factors. A limited number of economic analyses suggest that cardiac rehabilitation is also cost-effective.
- Most of this evidence derives from trials with only small numbers of patients older than 70–75 years of age.
- Future research programmes should therefore be aimed at specifically investigating the efficacy and effectiveness of cardiac rehabilitation in older, frail cardiac patients.

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SECTION 5

Respiratory Diseases

CHAPTER 46

Epidemiology of respiratory infection

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Community-acquired pneumonia

Many studies of community-acquired pneumonia (CAP) in the elderly have focused primarily on hospitalized cases. Marston *et al*.[1] evaluated all adults hospitalized for CAP in 1991 who resided in two counties of the State of Ohio in the USA. The incidence of CAP requiring hospitalization was 266.8 per 100 000 with an overall case-fatality rate of 8.8%. The incidence was higher in males and increased with age. Case-fatality was significantly higher in those ≥65 years of age (12.5%) compared with those aged <65 years (4.6%; $p < 0.001$). Kaplan *et al*.[2] performed a retrospective analysis of Medicare administrative data for 1997 and found that the overall incidence of CAP was 18.3 per 1000 population but increased from 8.4 per 1000 in those aged 65–69 years to 48.5 per 1000 in those aged 90 years and older, and the incidence was higher in males. Overall hospital mortality was 10.6% but mortality doubled with age from 7.8% in those 65–69 years to 15.4% in those 90 years and older.

Fry *et al*.,[3] using data from the National Hospital Discharge Survey in the USA, compared hospitalization rates for CAP among those aged 65 years and older between 1988 and 2002 and found that the rates increased by 20% for those aged 65–74 years and 75–84 years but not for those aged 85 years and older. However, rates of hospitalization were significantly higher in those aged 85 years and older compared with those aged 75–84 years. In a separate analysis of the National Hospital Discharge Survey from 1998 to 2003 there was an overall significant decrease in the rate of hospital discharges for invasive (meningitis and bacteraemia) pneumococcal disease; much of this invasive disease was likely related to pneumonia and most of the decrease was due to a decrease in discharge rates in those aged 65 years and older.[4] The overall decline in hospital discharge rate for invasive pneumococcal disease coincided with the introduction of the conjugated pneumococcal vaccine for children in 2000. The decline in incidence of invasive pneumococcal disease in those aged 65 years and older was also documented by the Active Bacterial Core Surveillance Program of the Centers for Disease Control and Prevention.[5]

Jackson *et al*.[6] provided the first extensive evaluation of rates of CAP in the elderly managed in the community and in the hospital. They evaluated 46 237 people age 65 years and older who were members of a health maintenance organization in one state in the USA between 1998 and 2001. Rates of CAP ranged from 18.2 episodes per 1000 person years for those aged 65–69 years to 59.9 per 1000 for those aged 90 years and older (overall rate 28.4 per 1000 person years). In all age categories, males had a higher rate of pneumonia episodes. In this population, 59% of all episodes of CAP were treated on an outpatient basis. Independent risk factors for CAP included older age, male gender, obstructive lung disease, asthma, diabetes, heart failure and smoking. Among persons hospitalized for treatment, 12.5% died within 30 days of admission whereas only 0.4% of persons treated as outpatients died within 30 days of initial diagnosis. O'Meara *et al*.[7] evaluated the rate of hospitalization for CAP in community-dwelling people aged 65 years and older enrolled in the Cardiovascular Health Study who were followed for a median of 10.7 years. Of 5888 enrollees, approximately 10% were hospitalized with CAP with a hospital mortality of 10%. Among those who survived the CAP episode, the risk of death in subsequent years was significantly higher compared with those with no CAP episodes. Significant predictors of hospitalization for CAP were age, male gender, smoking, history of cardiovascular disease, peripheral vascular disease, diabetes, chronic lung disease and race other than African-American. In a case–control study of community elderly patients enrolled in a health maintenance organization in one state in the USA, risk factors for CAP included presence and severity of cardiopulmonary disease, low weight or recent weight loss and poor functional status; 42% of CAP cases were said to be attributable to cardiopulmonary disease.[8]

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Nursing home-acquired pneumonia

In the nursing home setting, the reported incidence of pneumonia has ranged from 0.5 to 3.3 episodes per 1000 resident days in mostly retrospective studies.[9] The variation in the reported rate of nursing home-associated pneumonia (NHAP) may be related to differences in incidence over time, study design, number of facilities studied, completeness of case finding and facility affiliation (federal, community, proprietary, non-proprietary). Intensive prospective studies of NHAP found the incidence to be 0.7 to 1.0 episodes per resident care days.[9]

Multiple studies have identified risk factors for the development of nursing home-acquired pneumonia.[9] These factors include tracheostomy, dementia, dysphagia, tube feeding, depression, change in mental status, malnutrition/weight loss, poor functional status, chronic lung disease, smoking, no vaccinations, poor oral care, sedatives, cardiovascular disease, neurological disease, older age and male gender. The different risk factors that have been identified relate to variations in the definition of pneumonia/case finding, number of episodes studied, number of facilities studied and limitations in data collection/availability of data.

Risk factors for mortality among those with NHAP have been studied extensively. Comparison of the findings of these studies is problematic because some investigators combined pneumonia and bronchitis into a single group for analysis versus studies that focused on pneumonia. In addition, crude mortality varied depending on the site of treatment: 8.8–28% for those treated in a nursing home compared with 17.6–53% for those treated in hospital.[9] With these limitations in mind, the following factors were found to be significantly predictive of mortality: poor functional status, observed/history of aspiration, dementia, respiratory rate >30 breaths per minute, pulse >125 beats per minute, acute change in mental status and acute severity of pneumonia.[9] There is also evidence that there may be significant variations in mortality among facilities. Nicolle *et al*.[10] found significant variations in 21-day mortality in residents of 21 long-term care facilities in Canada prospectively identified with lower respiratory tract infection. This study utilized three different definitions of lower respiratory infection because of variations in diagnostic testing and reporting of clinical data among study facilities. Among the residents with chest radiographs demonstrating pneumonia, factors significantly associated with mortality were change in mental status from baseline, history of stroke, respiratory rate ≥25 breaths per minute, staffing level and number of hours dedicated to infection control efforts. This is the first study to identify facility-level factors that may be contributing to the outcome of NHAP.

Models to predict mortality among nursing home residents with lower respiratory tract infection[11] or with pneumonia[12] have been developed. Carusone *et al*.[13] found that the model developed by Naughton *et al*.[12] accurately predicted outcome only in the more severely ill group, whereas Nicolle *et al*.[10] found that mortality rates at higher predicted levels of severity were not accurately predicted utilizing the same model. van der Steen *et al*.[14] validated the model developed by Mehr *et al*.,[11] which requires laboratory testing that is not routinely performed in the nursing home setting.

Hospital-acquired pneumonia

The burden of hospital-acquired infections falls heavily on the elderly. Rates of hospital infection in general and hospital-acquired pneumonia in particular are significantly higher among the elderly than younger patients.[15] Despite the association between age and the development of hospital-acquired pneumonia, age alone is not the only reason for the increased risk; age may be a surrogate for serious underlying disease or debility, which, in turn, predisposes to pneumonia. In addition, life-saving interventions, such as intubation and mechanical ventilation, also increase the risk of pneumonia.

Tuberculosis

Despite advances in diagnosis, treatment and prevention, tuberculosis continues to cause significant morbidity and mortality worldwide.[16] It has been estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis* and that eight million people are identified with active tuberculosis each year and two million die yearly related to this infection.[17] The elderly continue to be a major reservoir for latent tuberculosis infection and active tuberculosis.[18] It has been estimated that 9.8% of sputum smear positive cases worldwide occur in those aged 65 years and older.[19] In an evaluation of data collected as part of the National Health and Nutrition Examination Survey (NHANES) in 1999–2000, a nationally representative sample of the civilian, non-institutionalized US population, it was estimated that the prevalence of latent tuberculosis infection was 5.6% in those 65 years of age and older; only those in the 45–64-year-old group had a higher prevalence (6.5%).[20]

In 2008, the incidence of tuberculosis in the USA was at a historical low of 4.2 cases per 100 000 population.[21] There was a significant decline in the incidence of tuberculosis in all age groups in the USA beginning in the mid-1990s through 2008. However, the incidence continues to be highest in those aged 65 years and older (6.4 cases per 100 000 in 2008) and 19% of cases in 2008 occurred in those aged 65 years and older.[21] In 2008, of 12 101 cases in which living situation was documented, 2.1% were reported to be in

residents of long-term care facilities.[21] Hence the burden of tuberculosis in the elderly in the USA continues to be substantial. The higher rate of tuberculosis in the elderly in the USA occurs in all racial and ethnic minorities.[16]

Non-influenza viral respiratory infection

Viral respiratory tract infections in general result in morbidity but minimal mortality in adults. In the elderly, however, viral respiratory infections can be more serious, resulting in outbreaks in congregative settings such as nursing homes or daycare centres for seniors with considerable morbidity and mortality.[22] Respiratory infection in this section refers to illnesses manifested primarily by one or more of the following symptoms: cough, nasal congestion, rhinorrhoea, sore throat, hoarseness, fever or wheezing with or without other constitutional symptoms.

Ruben *et al*.,[23] in a population-based study evaluating the development of infections among community-dwelling elderly, found that the overall rate of respiratory infection (including pneumonia) was three episodes per 100 person months of observation, with similar overall rates in males (2.9) and females (3.1) Specific rates of respiratory illnesses (per 100 person months) were common cold 1.3, bronchitis 0.9, otitis 0.2 and pharyngitis 0.1. Falsey *et al*.[24] found that in frail elderly attending a senior daycare programme the overall rate of acute respiratory infection was 10.8 episodes per 100 person months of observation, more than three times the rate for community-dwelling elderly described by Ruben *et al*.[23] Viruses were the most commonly identified aetiological agents, including respiratory syncytial viruses, influenza A virus and coronaviruses. The authors postulated that the higher rate of respiratory infection may be due to a more susceptible population and increased exposure to infectious agents in the daycare setting compared with the community setting.

Nicholson *et al*.[25] assessed the role of rhinovirus infection in a population of ambulatory elderly (60 years and older). Viral infection was documented in 43% of almost 500 episodes of respiratory infection and rhinovirus caused about half of these infections. In a separate analysis,[26] they found that lower respiratory symptoms related to rhinovirus infection in the elderly was significantly associated with current smoking, presence of chronic lung disease diagnosis or the presence of other underlying medical illness. Ellis *et al*.[27] studied residents of 381 nursing homes in Tennessee between 1995 and 1999 and found that respiratory syncytial virus infection increased hospitalization rates, antibiotic use and deaths each winter during the study. Agents such as rhinovirus and coronavirus that commonly cause colds in young adults or healthy elderly and are usually benign may result in hospitalization of frail elderly people with underlying cardiac or lung disease.[28] With the increasing use of molecular technology, an array of new viruses have been identified as causing respiratory illness in the elderly but their epidemiology remains to be elucidated.[29]

Key points

- The incidence of community-acquired pneumonia and associated case-fatality is highest in the elderly.
- Debilitated, bedridden people are at greatest risk for developing pneumonia in the nursing home setting.
- Rates of hospital-acquired pneumonia are higher in the elderly than younger people.
- The incidence of tuberculosis is highest in the elderly in developed countries, especially in the institutionalized setting.
- Common respiratory viral infections may produce severe illness in the frail elderly.

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CHAPTER 47

Pneumonia

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Introduction

Pneumonia is defined as an inflammatory process involving alveoli and terminal bronchioles and related to infectious agents. Infectious lung diseases and especially pneumonia are particularly serious in the elderly and represent the fifth leading cause of death in persons older than 65 years. Pneumonia is a major cause of hospitalization and about two of three patients hospitalized due to pneumonia are older than 70 years of age. The prognosis of pneumonia is severe, with a fatality rate reaching 50% in some series of nosocomial pneumonia.

Pneumonia should be differentiated from other lower respiratory tract infections and especially from acute bronchitis. Bronchitis is an inflammatory response of large bronchi with no involvement of the lung parenchyma. In contrast to pneumonia, bronchitis usually has a benign course, except in patients with chronic obstructive pulmonary disease who might suffer from deterioration of respiratory function.

Several factors may increase the risk of respiratory infection in the elderly (Table 47.1). During ageing, the body's defences against infectious agents are less effective, especially cellular immunity. The ageing respiratory system is particularly exposed to risks of infection because of reduced effectiveness of cough and mucociliary clearance and due to microaspiration. Some lung diseases commonly encountered in the elderly, for example, chronic obstructive pulmonary disease, asthma and sequelae of tuberculosis, may facilitate the occurrence of respiratory infection and also some common situations in geriatrics such as diabetes mellitus, heart failure, neurological diseases, swallowing disorders, use of sedative drugs, especially antipsychotics, gastro-oesophageal reflux, protein–energy malnutrition and enteral nutrition or nasogastric tube. Aspiration of oropharyngeal secretions and microflora, food debris or gastric contents is frequently involved in lower respiratory tract infection in frail elderly people, especially among patients having a neurological disease, dysphagia and/or using psychotropic drugs. Pneumonia is the main specific cause of mortality observed in Alzheimer's disease.

Causative agents

A wide variety of infectious agents may be responsible for respiratory infections in the elderly. Their identification is often difficult in the acute phase of infection, especially in frail elderly patients.

Many bacteria might provoke pneumonia. *Streptococcus pneumoniae* should be a major concern because it is the bacterium most commonly involved in community-acquired pneumonia requiring admission to hospital and its mortality rate is very high among the elderly. Other bacteria frequently involved are Gram-negative bacilli (especially in cases of aspiration, hospitalization or prior antibiotic treatment) and *Staphylococcus aureus. Legionella pneumophila* is rarer but often severe with a high mortality rate among elderly patients. The involvement of anaerobic bacteria seems fairly common, especially in aspiration-related pneumonia. Other bacteria may be involved, such as streptococci, staphylococci, Enterobacteriaceae, *Haemophilus influenzae* and *Mycoplasma pneumoniae*. Multimicrobial pneumonias are common in elderly patients. Hospital-acquired respiratory infections (nosocomial) are often severe because of the resistance of causative bacteria to certain antibiotics and because of the vulnerability of the patients, often weakened by the diseases that brought them to hospital. *Mycobacteria*, especially *M. tuberculosis*, can determine a subacute or chronic respiratory infection. Aspergillosis may be responsible for an infection in the pulmonary sequelae of tuberculosis or lung abscess. Fungal infections of the lung are very rare and relate to subjects with severe immunosuppression.

Viruses may be involved in 10–30% of community-acquired acute pulmonary infection and often occur in an epidemic, particularly in institutions. The agents involved

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Table 47.1 Conditions that favour respiratory infections in the elderly.

Ageing
Pulmonary diseases: chronic obstructive pulmonary disease, asthma, past tuberculosis
Diabetes mellitus
Heart failure
Neurological diseases
Swallowing disorders
Use of sedative drugs, especially antipsychotics
Gastro-oesophageal reflux
Protein–energy malnutrition
Enteral nutrition, nasogastric tube

are influenza (including in patients who received vaccination), respiratory syncytial virus, parainfluenza influenza, rhinovirus and adenovirus.

Patients' age and context of care are factors that influence the frequency of the agents responsible for pneumonia requiring hospitalization. In older patients, *S. pneumonia, H. influenzae* and respiratory viruses are more frequently observed than in younger adults, whereas *Legionella, Mycoplasma* and *Chlamydia* spp. are less frequent. In nursing home patients, aspiration pneumonia, Gram-negative enteric bacilli and multiple anaerobic agents are more frequently observed than in age-matched persons.

In hospital-acquired pneumonia (nosocomial), *S. aureus, Pseudomonas aeruginosa* and enteric Gram-negative bacteria are frequently observed, in addition to resistance to antibiotics. Also, pneumonia might be encountered in patients recently treated with antibiotics, together with complex and/or resistant germs including polymicrobial infection.

Clinical presentation of pneumonia in the elderly

The classical features of acute lobar pneumonia with general malaise, frank hyperthermia, cough and chest pain are rarely complete in the elderly: initially, fever and cough are absent in 30–40% of cases. In many cases, the picture is not typical, with a gradual onset of less marked signs leading to a delayed diagnosis. Elders with pneumonia usually have several respiratory or non-respiratory symptoms, but each of them might be missing. Respiratory symptoms comprise cough, productive or not, purulent sputum, dyspnoea, chest pain and haemoptysis. Non-respiratory symptoms usually comprise fever, anorexia, chills and sweats.

Examination of the patient can show the following findings: tachypnoea (respiratory rate $>30\,\text{min}^{-1}$) tachycardia (heart rate $>110\,\text{min}^{-1}$), fever and hypothermia. Classic auscultatory findings (localized crackles) are very suggestive of the diagnosis of pneumonia, but they may be absent or poorly recognized, because they are very discrete or because of hypoventilation or insufficient cooperation of the patient. The existence of wheezing indicating bronchial obstruction is common.

Other clinical presentations of pneumonia are possible. Severe sepsis with shock, hypotension, cold and clammy skin, altered consciousness and hypothermia should call for an examination of the lungs. Intestinal symptoms are sometimes prominent: abdominal pain, nausea, vomiting, paralytic ileus and diarrhoea. There can also be an isolated delirium or cardiac events such as onset of arrhythmia (atrial fibrillation) or heart failure.

Certain clinical presentations can suggest a specific aetiology. The flu syndrome with headache, diffuse myalgia, arthralgia, pharyngitis and rhinorrhoea orients towards a viral aetiology, especially in an epidemic context. The context of weight loss in recent weeks or months should prompt a search for tuberculosis.

Differential diagnosis of lower respiratory tract infection

Diseases whose clinical presentation can mimic that of pneumonia are numerous, and are outlined below.

Bronchitis

Bronchitis is frequently misdiagnosed as pneumonia. Acute bronchitis shares many symptoms with pneumonia, especially productive cough with purulent sputum. Usually, marked general signs are infrequent and there are no localized crackles. Classically, it is important to distinguish acute bronchitis from pneumonia (Table 47.2) because antibiotics are not indicated for bronchitis occurring in persons free from chronic obstructive pulmonary disease. In fact, in elderly subjects, the distinction between these two entities is sometimes difficult in the initial stage of infection. Indeed, in some subjects with pneumonia, temperature might be normal fever and may be missed and pulmonary auscultation might be difficult. Also, performing a chest radiograph is an important element in differentiating the two diseases. However, it is almost impossible to obtain a chest CT for every outpatient with symptoms of respiratory infection. A more feasible strategy consists in obtaining a chest radiograph 2–3 days after the beginning of the treatment in every patient with a suspected diagnosis of pneumonia: at present, the absence of a chest image suggestive of pneumonia should lead to the consideration of other diagnoses.

Exacerbation of chronic obstructive disease

Exacerbation of chronic pulmonary obstructive disease (COPD) might also be confounded with pneumonia. Exacerbation of COPD is defined by the worsening of

Table 47.2 Main findings in bronchitis and pneumonia.

	Bronchitis	Pneumonia
Marked asthenia, fever >38.5 °C, chills, tachycardia	Infrequent	Frequent
Cough	Yes	Yes
Increased respiratory rate at rest	Infrequent (except in COPD[a])	Frequent
Lung auscultation	Normal or diffuse wheezes	Localized crackles/wheezes
Leukocytosis	Normal or slightly increased	Normal or increased
Chest radiograph	Normal	Opacity or opacities, pleuritis (may be normal at a very early stage)
Chest computed tomography (CT)	Normal	Lung parenchymal opacities, pleuritis
Deterioration of a pre-existing condition	Infrequent (except in COPD)	Frequent

[a]COPD, chronic obstructive pulmonary disease.

cough, expectoration and/or dyspnoea and is easily recognized when COPD has been previously diagnosed. When the diagnosis of COPD has not been established, it is usually suspected by the association of smoking and a history of chronic bronchitis and dyspnoea. Exacerbations can be provoked by non-infectious causes, but also infectious causes including acute bronchitis or pneumonia. Antibiotics are indicated in severe exacerbations defined by an increase in dyspnoea and sputum purulence and volume, and also in exacerbation occurring in severe COPD with chronic respiratory failure.

Heart failure and pulmonary embolism

Heart failure associated with other infectious diseases (endocarditis, urinary tract infection) or a non-infectious disease responsible for fever may be confounded with pneumonia. Plasma brain natriuretic peptide (BNP) determination helps to distinguish dyspnoea related to heart diseases (BNP $>300\,\text{pg}\,\text{ml}^{-1}$) from that related to lung diseases. In elderly people, it is fairly common to observe concomitantly heart failure and pneumonia. Pulmonary embolism can share symptoms with pneumonia such as fever, cough, chest pain and dyspnoea. The normal lung fields on chest radiograph, the context favouring venous thromboembolism or the presence of clinical signs of venous thrombosis suggest the diagnosis of pulmonary embolism. The pulmonary infarction secondary to pulmonary embolism leads to signs shared with those of pneumonia and is very often the site of secondary infection.

Cancer and other diseases of the lungs

Lung cancer can be revealed by a respiratory infection. Massive loss of weight and marked anorexia, the persistence of the radiological image at 12 weeks after the infectious episode and high exposure to tobacco or asbestos are points that must lead to the consideration of the diagnosis of lung cancer and require bronchoscopy and/or a chest CT scan. Other diseases affecting the lungs can manifest the presentation of a lower respiratory tract infection: drug-related pneumonia (amiodarone, carbamazepine), lipid pneumonia (inhalation of a paraffin-based laxative), Wegener's granulomatosis, Churg–Strauss disease and other autoimmune diseases (rheumatoid arthritis, Sjögren's syndrome, coeliac disease). In these situations, the outcome after antibiotic treatment is not the same as that observed during a respiratory infection, which leads to consideration of these diagnoses and that of an infection resistant to prescribed antibiotics.

Hospitalization and further investigations in elderly persons with a suspected diagnosis of community-acquired pneumonia

Facing suspected pneumonia, physicians must quickly answer two questions:

- Should the patient be referred to hospital?
- Are additional tests required?

The answers to these questions depend on the severity of the disease, the patient's frailty and the context of care, and guide the type of treatment for the pneumonia.

Referral to hospital of an elderly person with suspected pneumonia

There are three main reasons that prompt referral to hospital.

First, the diagnosis of pneumonia is unclear and a severe disease is also suspected, such as pulmonary embolism or heart failure. In these conditions, the use of blood tests, ECG and chest X-ray is mandatory in order to select appropriate management.

Second, the diagnosis of pneumonia is likely, but conditions to treat the patient in their usual context of life (home

or nursing home) are not fulfilled. This applies not only for the administration of anti-infective treatment but also for general support of care such as help with activities of daily living, prevention of pressure sores and dehydration and for appropriate follow-up.

The third reason is related to the severity of pneumonia. This can be assessed using simple tools such as the CRB-65 scale (Table 47.3) or the pneumonia severity index (PSI). The scores given by these scales are indicators of mortality rates and can be used to identify low-risk patients who can be treated at home. Stratification of the risk given by the PSI is more precise than that given by the CRB-65. The CRB-65 is a simplified version of another scale, CURB-65, which contains an additional item related to plasma urea and is not suitable for the clinical assessment of patients without blood testing. Although the CRB-65 seems to be simpler, mental status requires the use of another scale, the Abbreviated Mental Test score, which includes 10 more items. The PSI items that can be obtained clinically are listed in Table 47.4. The PSI also contains biological variables which can be used in hospital settings. The Pneumonia Outcome Research Team (PORT) scale is a decision tree derived from the PSI to assess more accurately the mortality risk in young adults, but it is not relevant for older patients. Patients living in nursing homes often have a very high PSI score, owing to the importance of age and comorbid factors in the score. For instance, an 82-year-old man living in a nursing home and with a history of cerebrovascular disease will receive a PSI score of 102. With the CRB-65 scale, every elderly patient will receive at least one point, which indicates that referral to hospital should at least be considered in every elderly patient with suspected pneumonia.

Frail elderly patients with suspected pneumonia often fulfil the criteria for hospitalization for several reasons, such as loss of independence, high number of comorbidities, loneliness and uncertainty of the diagnosis and/or severity of pneumonia (Figure 47.1). Some complications, such as heart failure or acute respiratory failure, are frequent and severe in the elderly. Moreover, regardless of the severity of pneumonia, these patients are exposed to systemic complications such as dehydration, delirium, hyperglycaemia, bedsores and other complications of bed rest and usually require more intense support for activities of daily living during a severe infectious episode. Finally, as with any disease, severe acute respiratory infection in the elderly can cause diseases in cascades, by successive deterioration of chronic diseases that were hitherto balanced.

Table 47.3 The CRB-65 four-item scale to assess the severity of community-acquired pneumonia; each item counts 1 point if present and the CRB-65 score is the sum

- Confusion: new cognitive dysfunction according to Abbreviated Mental Test score
- Respiratory rate ≥ 30 min^{-1}
- Blood pressure: systolic <90 mmHg and/or diastolic ≤ 60 mmHg
- Age ≥ 65 years

If score = 3 or 4: high risk of mortality and urgent admission to hospital is required

If score = 1 or 2: consider hospital referral (especially in a patient with score = 2)

If score = 0 (not applicable in the elderly): treatment at home

Table 47.4 Pneumonia severity index (PSI) simplified for patients aged 65 years or more, clinically assessed without laboratory test results.

Patient characteristics	Points assigned	Patient's points
Age (years)		
Man	Age	
Woman	Age–10	
Nursing home resident	+10	
Comorbidities		
Neoplastic disease	+30	
Liver disease	+20	
Congestive heart failure	+10	
Cerebrovascular disease	+10	
Renal disease	+10	
Initial examination findings		
Altered mental status	+20	
Respiratory rate ≥ 30 min^{-1}	+20	
Systolic BP <90 mmHg	+20	
Temperature <35 or $\geq 40\,^{\circ}$C	+15	
Pulse ≥ 125 min^{-1}	+10	
SaO_2 $<90\%$ (if oxymeter available)	+10	
Score = sum of points		
Score range	*Site of treatment*	*Mortality range (%)*
<70	*Outpatient*	*0.6–0.7*
71–90	*Outpatient*	*0.9–2.8*
91–130	*Inpatient*	*8.2–9.3*
>130	*Inpatient*	*27–29*

Are additional tests required?

Additional investigations to assess the severity of infection and to seek its origin should be widely pursued in severe pneumonia requiring admission to hospital due to pneumonia and in pneumonia acquired in hospital.

Chest imaging

Lung imaging shows the involvement of lung parenchyma that is a major factor in documenting a gold standard

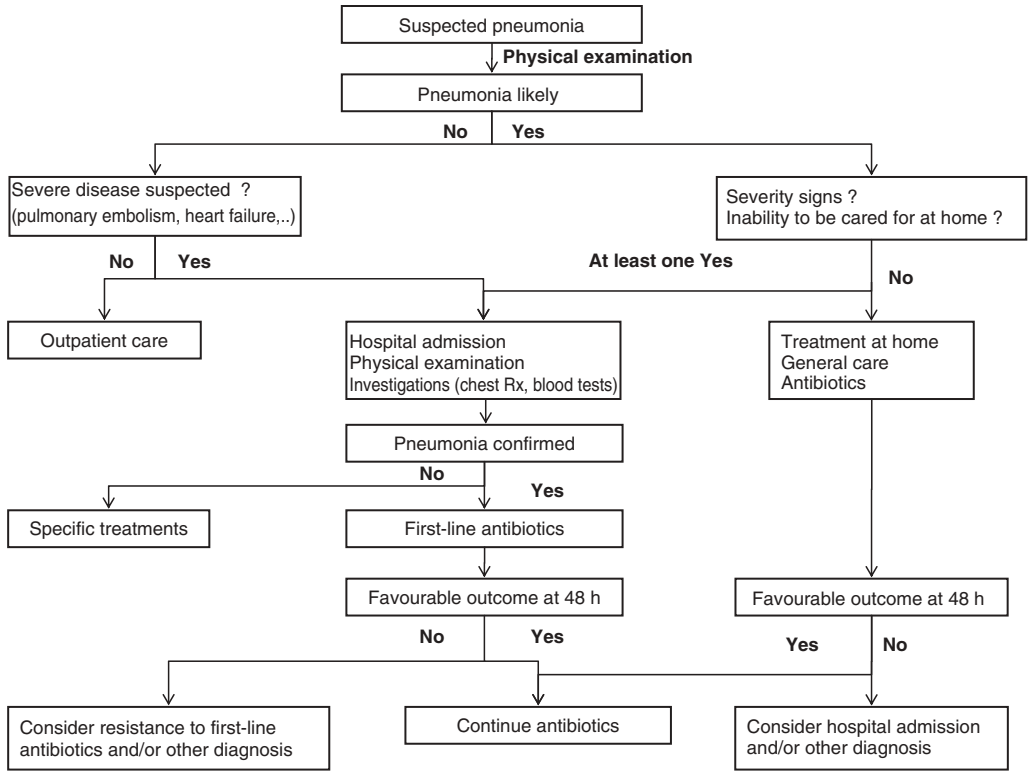

Figure 47.1 Decision tree for hospitalization of frail elderly patients with suspected pneumonia.

diagnosis of pneumonia. The front and lateral chest radiographs search for systematized alveolar-type condensation or a mixed alveolar and interstitial image, less systematized atelectasis or microatelectasis, a peri-hilar interstitial diffuse, interstitial or localized image and more or less systematized. The radiographic type is poorly related to the infectious agent. The absence of a visible parenchymal focus usually indicates the absence of parenchymal infection (bronchitis), but might be observed in acute pneumonia at a very early stage (pneumococcal pneumonia). Chest images should be carefully examined for a discrete image or inconspicuous image, especially retro- or pericardial. A CT scan is indicated in situations difficult to document as parenchymal.

In their guidelines on low respiratory infections, the European Thoracic Society recommends obtaining a chest X-ray in every patient with suspected pneumonia, mainly to differentiate pneumonia from bronchitis. However, it is very difficult to implement this recommendation in every old patient living in the community or living in a nursing home. The guidelines of the British Thoracic Society propose managing patients with community-acquired respiratory infection without a chest X-ray if the diagnosis of pneumonia is likely and if the patient does not require hospital admission. Of course, in patients referred to hospital for suspected pneumonia, whatever the reason, a chest X-ray is recommended to confirm the diagnosis of pneumonia.

In difficult cases and especially when pneumonia is suspected despite a normal chest X-ray, a chest CT scan might help identify pneumonia at a very early stage or pulmonary embolism.

Biological tests

Biological tests and in particular microbiological tests are not recommended for patients having pneumonia which can be managed out of hospital. Biological tests are performed on hospitalized patients with pneumonia.

A blood cell count often shows leukocytosis with neutrophils, which suggests a bacterial origin. However, leukocytosis may be lacking in older patients with bacterial infections, including pneumonia. A frank increase in C-reactive protein is also supportive of a bacterial origin. Electrolytes, urea, creatinine and glycaemia should be measured since abnormalities related to dehydration, renal failure or hyperglycaemia are common. The measurement of oxygen saturation by finger sensor is a simple and non-invasive test that evaluates an immediate impact on the haematosis. In cases of chronic respiratory failure, cyanosis, sweating or loss of consciousness, arterial blood gas should be measured.

Microbiological tests aim to identify the infectious agent. These tests should be widely applied, although it is unusual to obtain immediate findings to guide the choice of fist-line anti-infective drugs. However, they are very useful, especially in cases where the infectious syndrome is not controlled by the first-line drugs. Blood cultures and sputum examination should be carried out in all patients referred to hospital due to pneumonia. Blood cultures may isolate the causative organisms associated with bacteraemia. Bacteriological examination of sputum can be helpful in highlighting unusual germs found in the oral commensal flora, such as pneumococcal or *Legionella* species. It is often difficult to achieve an appropriate sampling of sputum in asthenic or uncooperative patients, although it is essential to obtain secretions from the lower respiratory tract.

A search for pneumococcal urinary antigen or *Legionella* is not recommended immediately in community-acquired pneumonia, except in the context of clinical suspicion or outbreak. This search is recommended in cases of very severe pneumonia which required treatment in an intensive care unit. Urine microscopic examination and culture are not useful in older patients with pneumonia and should not be performed, as they might lead to the finding of bacteria unrelated to respiratory infection due to the high prevalence of asymptomatic bacteriuria and in turn wrongly influence physicians prescribing antibiotics.

Respiratory virus testing is rarely performed in the context of community-acquired infection. In the case of an epidemic occurring in a geriatric facility, a search for respiratory viruses should be made at least in some patients to identify the virus responsible for the epidemic. The procedure of choice is nasal swab. Rapid tests are able to diagnose influenza within hours, whereas conventional viral culture requires 48 h or longer.

Mycobacterium tuberculosis should be searched for in pneumonia associated with weight loss or deterioration of the general condition occurring over several weeks or even months. Suitable samples for examination can be the sputum, gastric fluid or the material aspirated during bronchoscopy. The Mantoux test suggests active tuberculosis when it leads to a large induration with blebs. In case of simple positivity or negativity, it does not confirm or exclude the diagnosis of active pulmonary tuberculosis. The value of the QuantiFERON test or other interferon release assays has not been extensively documented for the diagnosis of active tuberculosis in very old people, many of whom had contact with the germ during their lifetime.

Serological tests are available for the identification of *Legionella, Chlamydia, Mycoplasma* and respiratory viruses. If used, they should be repeated two weeks later. They might be useful for retrospective diagnosis.

Therapy of pneumonia in the elderly

General measures

Some measures are not specific and relate to the management of conditions commonly associated with respiratory infection in the frail elderly, such as dehydration, anorexia and immobilization. They include oral hydration, oral nutritional supplementation if the patient is malnourished, oral care and prevention of pressure ulcers. Intravenous or subcutaneous fluids are often necessary in the case of dehydration. Antipyretics should be given, unless fever $>39.5\,^{\circ}C$ is poorly tolerated. Delirium is frequent and should be managed by non-pharmacological approaches. Venous thrombosis and pulmonary embolism should be prevented with subcutaneous heparin unless contraindicated. Appropriate control of comorbid conditions is also an important objective of the treatment.

Non-infectious treatments for pneumonia

Oxygen therapy by the nasal route is indicated in acute cases whenever there is dyspnoea and/or hypoxaemia, but should be used with caution in cases of chronic respiratory failure with hypercapnia. Respiratory physiotherapy is useful and aims to improve breathing and abdominal drainage of bronchial secretions. Inhaled bronchodilators by β_2-agonists and anticholinergics should be used if signs of bronchial obstruction are present. In bronchial obstruction resistant to inhaled bronchodilators, short-course systemic corticosteroids may improve ventilatory status. The occurrence of a large atelectasis inducing a sudden worsening of dyspnoea is an indication for emergency bronchoscopy for detection of mucus plugs and guided aspiration.

First-line anti-infective agents

Choice of antibiotics

Fist-line antibiotic treatment of bacterial pneumonia depends on the context of care, the severity of the disease and the germs suspected. However, the choice of initial antibiotic treatment remains largely probabilistic unless the causative agent has been identified. Hence it is important to assess the adequacy of initial antibiotic therapy after 48 h, depending on the patient's clinical response and early results of microbiological tests.

For community-acquired bacterial pneumonia, initial antibiotic therapy must be effective on the pneumococcal and *Haemophilus influenzae* species that are the most frequently observed in this context. First-line antibiotics recommended for community-acquired pneumonia in persons with comorbid conditions (which applies to most elderly persons) who do not require admission to hospital are listed in Table 47.5. In most cases, a single oral

Table 47.5 First-line antimicrobial therapy recommended for patients with comorbidities with community-acquired pneumonia treated in the community.

Guidelines	First-line antimicrobial therapy	Alternative choice
American Thoracic Society (ATS) (2001)	[Macrolide or doxycycline] *Plus* β-lactam (oral cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin–clavulanate; or parenteral ceftriaxone followed by oral cefpodoxime)	Anti-pneumococcal fluoroquinolone[a] (used alone)
Infectious Diseases Society of America (2003)	Azithromycin *or* clarithromycin *or* respiratory fluoroquinolone[a]	
European Respiratory Society (2005)	Amoxicillin *or* doxycycline	Amoxicillin–clavulanate *or* macrolide *or* levofloxacin (*or* moxifloxacin[b])
Société de Pathologie Infectieuse de Langue Française (2006)	Presumed viral pneumonia during a period of influenza circulation: neuraminidase inhibitors	
	Presumed bacterial pneumonia: amoxicillin–clavulanate (1 g×3 per day)	Presumed bacterial pneumonia: levofloxacin 500 mg per day (*or* moxifloxacin[b])
British Thoracic Society (2009)	Amoxicillin 500 mg×3 per day	Doxycycline *or* clarithromycin

[a] Moxifloxacin, levofloxacin or gemifloxacin.
[b] Use of moxifloxacin has recently been restricted due to adverse effects.

antibiotic can be used: amoxicillin, amoxicillin–clavulanate, an advanced macrolide (azithromycin or clarithromycin), doxycycline or a respiratory fluoroquinolone (levofloxacin, gemifloxacin or moxifloxacin).

In nursing home patients with pneumonia, recommended first-line antibiotics are listed in Table 47.6. Since aspiration pneumonia is frequent in such settings, these regimens should be active against anaerobic bacteria. However, within the ATS recommendation, the regimen constituted by cephalosporin (or high-dose amoxicillin) plus macrolide might not be active against anaerobic bacteria.

Table 47.6 Choice of first-line antibiotics for treatment of community-acquired pneumonia in nursing home patients.

Guidelines	First-line antibiotics
SPILF	Oral amoxicillin–clavulanate (1 g ×3 per day) *or* parenteral ceftriaxone *or* oral levofloxacin (500 mg per day) *or* oral moxifloxacin (400 mg per day)
ATS	[Intravenous β-lactam (cefotaxime, ceftriaxone, ampicillin–sulbactam or high-dose ampicillin) *plus* (intravenous or oral macrolide or doxycycline)] *or* [intravenous anti-pneumococcal fluoroquinolone alone]
IDSA	Respiratory fluoroquinolone alone *or* [oral amoxicillin–clavulanate *plus* (azithromycin or clarithromycin)]

Abbreviations: see Table 47.5

In severe community-acquired pneumonia and in hospital-acquired pneumonia, the use of a broad-spectrum antibiotic regimen is appropriate and the choice depends on prior antibiotics (β-lactam or fluoroquinolone in the past three months) and risk factors for *Pseudomonas* (bronchiectiasis, corticosteroids, recent broad-spectrum antibiotic treatment in the past month, malnutrition) or for other agents (immunosuppression). In these cases, several regimens can be proposed, such as a parenteral third-generation cephalosporin (or *Pseudomonas*-active cephalosporin) associated with a macrolide; a parenteral respiratory fluoroquinolone alone or with a third-generation cephalosporin; imipenem–cilastatin; or piperacillin–tazobactam. Metronidazole or ornidazole should be added to antibiotic regimens which are not active against anaerobic bacteria. In these complex cases, the advice of an infectious disease specialist is important.

When the diagnosis of influenza pneumonia is suspected, the use of neuraminidase inhibitors should be discussed if the symptoms of infection are recent (<48 h). This condition is infrequently encountered except for new cases of pneumonia occurring during an influenza-proven outbreak in a geriatric institution. Oral oseltamivir is preferred in elderly patients with pneumonia, because administration is easier than with inhaled zanamivir.

Handling anti-effective agents in the elderly

When prescribing anti-infective drugs in older patients, it is important to consider the patient's renal function, concomitant drug treatments and previous allergy/intolerance

to antibiotics. The dosage of some anti-infective agents should be reduced in patients with creatinine clearance $<30\,ml\,min^{-1}$: amoxicillin, cefuroxime, ceftazidime, imipenem, ciprofloxacin, levofloxacin, clarithromycin, erythromycin, metronidazole, aminosides and oseltamivir. Drug–drug interactions should be considered mainly with macrolides (warfarin, digoxin, statins).

Antibiotics should be given by the oral route, except in severe infections where the parenteral route is preferred. The intravenous route is the most frequently used, but it should be noted that ceftriaxone can be given by subcutaneous injection.

Follow-up of patients

The 48 h assessment

The expected response to antibiotic therapy is expected to occur within 2–4 days after the beginning of the treatment. Assessment after 48 h of the first-line antibiotic therapy is a very important step. Fever decrease and clinical stability or improvement indicate a favourable response to treatment. In this case, oral antibiotic therapy should be continued and, if parental antibiotics have been used, they should be switched to oral antibiotics of the same pharmacological class. At this time, results of microbiological testing (if done) are available and if positive might influence the course of the treatment.

Management of patients with an unfavourable response is more difficult. Referral to hospital should be proposed to those treated in outpatient settings. Several possibilities should be discussed: pneumonia due to microorganisms resistant to the antibiotics given (including virus or tuberculosis), encysted pleural effusion, non-infectious lung disease, adverse effects of antibiotics or worsening of comorbid conditions. Clinical examination, blood testing, chest X-ray and chest CT scan help in investigating these issues. A search for urine antigen is indicated, if it has not yet been done. Antibiotics should be modified if bacterial infection resistant to the first antibiotic regimen is suspected. The advice of an infectious disease specialist should be obtained if possible.

Further follow-up

The total duration of antibiotic administration is about 10 days, except for azithromycin, which can be used for 5 days. Usually, fever disappears and leukocytosis and C-reactive protein decrease during 2–5 days after the beginning of the treatment. Cough persists longer, but sputum volume and purulence decrease.

In patients for whom the antibiotic regimen was changed at the 48 h assessment, a 10 day duration for the new antibiotic regimen is appropriate. In these patients, an unfavourable outcome during the second antibiotic course is a difficult situation, which should be managed by lung and infectious disease specialists. A search for microorganisms in a more invasive manner, should be reconsidered even after stopping the antibiotics if possible.

In patients with a favourable clinical outcome, it is not necessary to perform a chest X-ray to document the disappearance of the lung opacities. Regression of lung images takes longer in elderly people and might require up to 12 weeks. If a lung cancer associated with pneumonia is then suspected, a chest CT scan and bronchoscopy should be performed.

Prevention of pneumonia in the elderly

The main ways to prevent pneumonia in the elderly are summarized in Table 47.7. Influenza vaccination is indicated in all persons aged 65 years or more. It must be performed each year in early autumn. It can reduce by 50% the risk of developing influenza and by 70% the mortality due to influenza. In France, the vaccine is offered free to all persons aged over 65 years. This vaccine is well tolerated and rarely leads to minor local reactions and systemic reactions. The adjuvant influenza vaccine contains of a substance that stimulates the immune response and enhances the immunogenicity of the vaccine and their use is particularly valuable in the elderly living in institutions and/or weakened by a chronic disease such as diabetes or heart or respiratory failure. Influenza vaccination of healthcare personnel in long-term care settings possibly reduces the incidence of respiratory infection and overall mortality among residents of these institutions, even when the vaccination coverage rate of residents for influenza is high. Health authorities recommend influenza vaccination largely of healthcare personnel in regular contact with elderly patients. It should also encourage employers to offer such personnel easy access to free vaccination. It is logical to recommend the same protection to regular visitors of residents, including family members, stakeholders and staff volunteers.

Table 47.7 Prevention of pneumonia in the elderly.

For elders
Anti-pneumococcal vaccine every 3–5 years
Influenza vaccine each year
If swallowing disorders: treatment and rehabilitation
Avoid sedative drugs (antipsychotics)
Avoid contacts with persons having a respiratory infection and cough or rhinitis
Ask them to wear a facemask
For healthcare staff (and relatives with frequent contacts)
Influenza vaccine each year
If respiratory infection and cough or rhinitis: wear facemask, avoid contacts with elderly people and strengthen hand hygiene

When an outbreak of respiratory infection occurs in a geriatric institution, a search for germs, in particular influenza virus, should be carried out. In influenza outbreaks, the use of neuraminidase inhibitors (oseltamivir in particular) is recommended for cases and also for contacts to stop the outbreak. Given the number needed to treat, the role of influenza virus should be documented by laboratory diagnosis tests.

If an outbreak of influenza occurs in an institution, influenza vaccination should be offered to unvaccinated residents and staff, visits and movement of residents in the institution should be temporarily restricted and group activities should be temporarily stopped. Hand hygiene should be reinforced and residents and staff with symptoms should wear masks. Some of these measures are difficult to implement given the cognitive status of some residents and organizational constraints related to the institution, such as service of meals in a collective dining room. In case of an outbreak of viral pneumonia not related to influenza virus, the same general measures are recommended, but there is no vaccination and/or antiviral treatment.

Pneumococcal vaccination is indicated in all elderly persons living in geriatric institutions and in the elderly living at home and weakened by chronic illness (heart failure, respiratory failure, diabetes). This was shown to reduce the incidence of invasive pneumococcal disease, but its efficacy in preventing pneumonia has been the subject of debate. Recently, a large-scale randomized trial in Japanese nursing homes found a marked decrease in mortality and in pneumonia incidence among vaccinated groups.

Swallowing disorders should be subjected to careful management, ideally guided by a speech therapist. It is important to look systematically at patients with neurological diseases. Initially, adaptation of food is sometimes sufficient: thicker liquids are better tolerated, and also small bites or sips. Water gel can help to maintain hydration when swallowing liquids is difficult. When these small means are insufficient, long-term enteral nutrition by percutaneous gastrostomy should be discussed on a case-by-case basis, knowing that this technique does not protect against the risk of respiratory infection by inhalation and if it fits in an ethical approach. Avoiding unnecessary sedative drugs (in particular benzodiazepines and neuroleptics) and dosage reduction might help to prevent aspiration.

Key points

- Pneumonia is a major cause of hospitalization and about two out of three hospitalizations due to pneumonia are of patients over 70 years of age.
- Pneumonia should be differentiated from other lower respiratory tract infections, especially bronchitis.
- Numerous infective agents provoke pneumonia, especially bacteria and viruses.
- Referral to hospital and further tests are important questions to be decided.
- Therapy includes non-infective treatments and anti-infective agents such as antibiotics.
- Preventive measures include anti-pneumococcal vaccine and influenza vaccine.

Further reading

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CHAPTER 48

Aspiration pneumonia

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Aspiration pneumonia and aspiration pneumonitis

Pneumonia is a common cause of death among older people despite the availability of potent novel antimicrobials. Whereas the death rate of juvenile pneumonia has decreased nearly to zero, that of old people has remained unchanged over the past 100 years. In other words, the traditional approach has proven a limited success: as Osler put it over 100 years ago, 'pneumonia is actually a friend to the old'.[1] Both the increased incidence of pneumonia and high mortality among older people are a consequence of a number of age-related factors including coexisting illnesses, therapeutic interventions and decreased host defence mechanisms. In these, aspiration is possibly the most important risk factor for pneumonia in the elderly.[2] Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and the lower respiratory tract. Several pulmonary syndromes may occur after aspiration, depending on the amount and the nature of the aspirated material, frequency of aspiration and the host's response to the aspirated material.[3] Aspiration pneumonia is an infectious process caused by an inhalation of the oropharyngeal secretions that are colonized by pathogenic bacteria, whereas aspiration pneumonitis including Mendelson syndrome is a chemical injury caused by an inhalation of sterile gastric contents.[3] Although there is some overlap between these syndromes, they are distinct clinical entities. This chapter focuses on the pathophysiology and the management of aspiration pneumonia and aspiration pneumonitis.

Mechanisms for development of aspiration pneumonia or aspiration pneumonitis

Aspiration pneumonia

Pneumonia in the elderly is often caused by a non-apparent swallowing disorder.[2] Such 'silent aspiration' frequently occurs and is a more important cause of pneumonia than acute aspiration of gastric content in older people.[4] Silent aspiration of oropharyngeal bacterial pathogens to the lower respiratory tract is an important risk factor for community-acquired pneumonia[5] and also nosocomial pneumonia in the elderly.[6] Normal hosts are less likely to develop pneumonia because they aspirate smaller volumes or are able to clear bacteria rapidly.[7] However, an extremely small volume (0.01 ml) of saliva contains pathogenic numbers of bacteria.[7] Elderly patients with a predisposition to aspiration frequently aspirate oropharyngeal secretions and the development of pneumonia occurs when normal pulmonary defence mechanisms are overwhelmed.[8] Adequate protective reflexes in the airway are important and suppression or absence of these reflexes has led to pneumonia.[8] For example, Nakajoh *et al*. reported that the incidence of pneumonia was higher in patients having both a latency of swallowing response longer than 5 s following stimulation with 1 ml of distilled water and a cough threshold for inhalation of citric acid aerosol higher than a concentration of 1.35 (log mg ml^{-1}).[9] Thus, the progressive loss of protective reflexes (i.e. swallowing and cough reflexes) with age is thought to be one of the mechanisms for aspiration pneumonia, which is often seen in older people.[10] In fact, impaired swallowing and cough reflexes have been shown in patients suffering from aspiration pneumonia.[11] However, re-evaluation of age-related changes in protective reflexes in individuals who lead active daily lives has shown that both reflexes do not decrease with the advance of age,[12,13] indicating that involutional and degenerative changes associated with ageing often result in marginally compensated protective reflexes.[14] Disorders of the central nervous system are more likely to develop in the elderly and pneumonia has been estimated to occur in about one-third of patients with stroke.[15] The most important factor contributing to the development of pneumonia in patients with stroke is suggested to be dysphagia with aspiration.[16] Nakagawa *et al*. have shown that the risk of

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pneumonia was significantly higher in patients with basal ganglia infarcts than in patients with or without cerebral hemispheric strokes in other locations.[8] They found that multiple episodes of pneumonia occurred only in patients with bilateral basal ganglia infarcts and that there was a higher mortality rate associated with pneumonia in these patients.[8] Delayed triggering of the swallowing reflex occurs in patients with infarcts in the basal ganglia.[14] These results strongly suggest that disruption of basal ganglia functions is critically important in the development of aspiration pneumonia. The pharyngeal, laryngeal and tracheal epithelia, the most important sites for the initiation of swallowing and cough reflexes, have an extensive plexus of nerves that contains substance P.[17,18] Capsaicin desensitization, which diminishes substance P from the airway and upper digestive tract, or an administration of neurokinin (NK)-1 receptor antagonist remarkably attenuated the cough response to tussive stimuli[19,20] and distilled water-induced swallowing reflex in guinea pigs,[21] suggesting an important role of substance P-containing nerves in the initiation of these protective reflexes. Thus, irritation of laryngeal and pharyngeal mucosa by stimuli may activate capsaicin-sensitive sensory nerves, releasing substance P, with the result that protective reflexes are initiated by stimulation of the glossopharyngeal and vagal sensory nerves.[19] Treatment with a dopamine agonist in the rat brings about a heightened striosomal expression of substance P and both dopamine D1 and D2 antagonists decrease substance P.[22] Mice lacking the dopamine D1 receptor[23] and those treated with dopamine D1 receptor antagonist[24] showed abnormal motor activities and feeding and swallowing problems. An impairment of dopamine metabolism in the basal ganglia is observed in patients with infarcts in the basal ganglia.[25] Taking these facts together, the mechanisms of silent aspiration may be speculated as shown in Figure 48.1. Patients with basal ganglia infarcts may suffer from reduced dopamine metabolism, which decreases substance P in the glossopharyngeal and vagal sensory nerves. Reduction in substance P concentration in these nerves impairs both swallowing and cough reflexes, which increases the frequency of silent aspiration. Because the action of swallowing and coughing is a fundamental defence mechanism against aspiration of oropharyngeal contents into the respiratory tract, impairment of both reflexes is one of the major reasons for the development of aspiration pneumonia (see Figure 48.1). In patients with aspiration pneumonia, unlike those with aspiration pneumonitis, the episode of aspiration is generally not witnessed. The diagnosis is therefore inferred when a patient at risk for aspiration has radiographic evidence of an infiltrate in a characteristic bronchopulmonary segment. Elderly persons frequently receive poor oral care, resulting in oropharyngeal colonization by potential respiratory tract pathogens, including Enterobacteriaceae, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. These pathogens are aspirated and may cause pneumonia.[3]

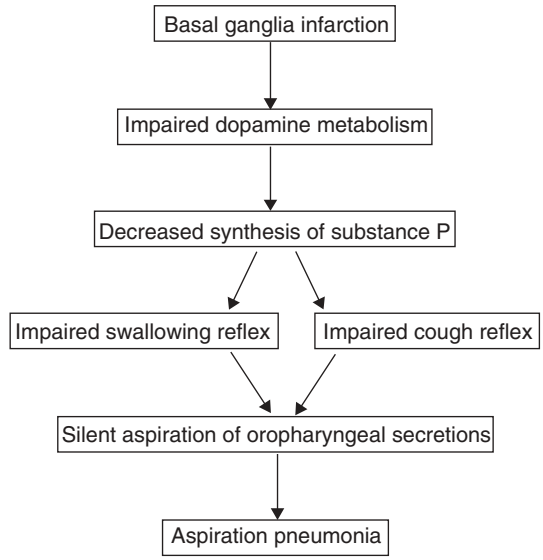

Figure 48.1 Possible mechanisms for development of aspiration pneumonia in patients with basal ganglia infarction.

Aspiration pneumonitis

Aspiration pneumonitis is defined as acute lung injury after the inhalation of regurgitated sterile gastric contents. This syndrome occurs in patients who have a marked disturbance of consciousness such as that resulting from a drug overdose, seizures, a massive cerebrovascular accident or the use of anaesthesia.[3] The syndrome most commonly described as aspiration pneumonitis is Mendelson syndrome.[26] Reflux of gastric fluids into the airway can damage the respiratory tract.[27] Marked damage to the tracheal mucosa can occur even when the volume of aspirated gastric fluid is too small to cause clinically significant aspiration pneumonitis and repeated long periods of aspiration of gastric fluid may even cause interstitial pulmonary fibrosis. Damage is always more severe when the pH of the gastric contents is low, but gastric fluid also contains substances other than acid which cause airway damage and delay healing of the airway epithelial damage.[3,27] Since airway epithelial damage by gastric content probably arises from the additive effects of acidity,[27] treatment of gastroesophageal reflux using antiacids such as histamine-H2 receptor antagonists alone may not improve symptoms caused by aspiration of gastric fluids.[3]

Treatments for aspiration pneumonia and aspiration pneumonitis

Aspiration pneumonia

Antibiotic therapy is unequivocally indicated in patients with aspiration pneumonia. The choice of antibiotics should depend on the setting in which the aspiration occurs and also the patient's general health. However, antibiotic agents with activity against Gram-negative organisms, such as third-generation cephalosporins, fluoroquinolones and piperacillin, are usually required.[3] Kanda *et al*. evaluated an additive effect of angiotensin-converting enzyme (ACE) inhibitor and amantadine to the conventional antibiotic therapy for pneumonia and found that the combined administration of these drugs can shorten the duration of hospitalization and antibiotic use, inhibit methicillin-resistant *Staphylococcus aureus* (MRSA) infection and lower the medical cost for treatment of pneumonia.[28]

Aspiration pneumonitis

Although it is common practice, the prophylactic use of antibiotics in patients in whom aspiration is suspected or witnessed is not recommended.[3] However, empirical antibiotic therapy is appropriate for patients who aspirate gastric contents and who have small-bowel obstruction or other conditions associated with colonization of the gastric contents.[3] Antibiotic therapy should be considered for patients with aspiration pneumonitis that fails to resolve within 48 h after aspiration. Empirical therapy with broad-spectrum agents such as fluoroquinolone or piperacillin is recommended. Corticosteroids have been used for decades in the management of aspiration pneumonitis. However, there are limited data on the role of these agents.[29]

Strategies for the prevention of aspiration pneumonia (Figure 48.2)

Pharmacological therapy

Capsaicin

Because substance P is a neurotransmitter of the swallowing reflex and is depleted in patients with aspiration pneumonia,[30] capsaicin, a pungent substance in red peppers that stimulates sensory nerves, may improve the swallowing reflex in these patients.[2] Ebihara *et al*. measured the swallowing reflex with a bolus injection of 1 ml of distilled water into the pharynx through a nasal catheter and suggested that the addition of a low dose of capsaicin to liquid or food may stimulate the swallowing reflex and help to prevent aspiration pneumonia in the elderly.[31]

1. Pharmacological therapy
   a. Capsaicin
   b. Angiotensin-converting enzyme inhibitors
   c. Dopamine and amantadine
   d. Cilostazol
   e. Folic acid
   f. Menthol
   g. Banxia houpu tang
   h. Black pepper oil
   i. Mosapride
2. Oral hygiene
3. Sitting position
4. Avoid neuroleptics
5. Handwashing

Figure 48.2 Preventive strategies for aspiration pneumonia.

Angiotensin-converting enzyme (ACE) inhibitors

A well-known adverse effect of ACE inhibitors is a dry cough.[32] Since substance P is degraded by ACE,[33] its action is potentiated by ACE inhibitors.[34] Using ACE inhibitors, substance P might accumulate in the upper respiratory tract because of inhibited ACE activity and cause an increase in the sensitivity of the cough reflex.[2,20] In a similar way to the cough reflex, ACE inhibitors improve the swallowing reflex in older patients with aspiration pneumonia.[2] Sekizawa *et al*. compared the rate of pneumonia in stroke patients with hypertension treated by ACE inhibitors with that in stroke patients treated by other antihypertensive drugs and found that the risk of pneumonia is reduced by about one-third if ACE inhibitors are used for hypertension compared with the use of other antihypertensive drugs.[35] ACE inhibitors, therefore, may have beneficial effects on the prevention of pneumonia in these patients. Arai *et al*. reported that the rate of pneumonia was significantly lower in elderly hypertensive patients given ACE inhibitors than that in those treated with calcium channel blockers.[36] However, Teramoto and Ouchi refuted the advantage of ACE inhibitors over calcium channel blockers in preventing pneumonia in adult and elderly subjects with hypertension.[37] In elderly individuals, the severity of the underlying cerebrovascular disease greatly affects susceptibility to pneumonia. ACE inhibitors could be useful in the prevention of aspiration pneumonia in elderly patients with stroke but not in those without stroke.

Dopamine and amantadine

Delayed triggering of the swallowing reflex occurs in patients with basal ganglia infarctions[2] and an impairment

of dopamine metabolism in the basal ganglia is observed in these patients.[25] Kobayashi *et al*. investigated whether levodopa improves the swallowing reflex in patients with basal ganglia infarctions who had a history of aspiration pneumonia.[38] The subjects were given an intravenous drip infusion of levodopa (50 mg in 20 ml of saline) for 30 min. They found that the administration of levodopa improved the impaired swallowing reflex in these patients. Since dopamine supplementation improves the swallowing reflex in patients with cerebral infarctions, Nakagawa *et al*. investigated whether amantadine, a drug that acts as a dopamine releaser from dopaminergic nerve terminals, lowers the incidence of pneumonia in patients with cerebral infarctions.[39] Patients were randomly assigned amantadine 100 mg per day or no active treatment and were investigated for 3 years. During follow-up, the relative risk of developing pneumonia in patients on no active treatment compared with that in those on amantadine was 5.92. These findings suggest that the risk of pneumonia is lowered by about 20% if amantadine is used in patients with previous stroke. Amantadine may, therefore, have beneficial effects on the prevention of pneumonia in these patients. Of course, other recognized effects of amantadine might also have impacted the incidence of pneumonia in these studies. For example, amantadine improves the conscious state in patients with brain injury[40] and more active stroke patients may be less likely to aspirate. In addition, dopaminergic receptors have been identified in the lower oesophageal sphincter and amantadine might reduce gastroesophageal reflux[41] and thereby lower the risk of aspiration pneumonia. Finally, antiviral effects and prevention of influenza infection might also lower the incidence of pneumonia over a 3 year period. Hence the mechanism by which amantadine might positively affect the incidence of pneumonia remains to be proven.[42]

Cilostazol

Disorders of the central nervous system including dementia and atherosclerotic cerebrovascular disease are more often associated with aspiration than other specific neuromuscular disorders.[2] The mechanisms by which brain injury affects the risk of aspiration are beginning to be delineated. For example, in healthy people, the frequency of swallowing during sleep is slightly less than that when awake,[43] but severe delay of the swallowing reflex during nighttime compared with that during daytime was observed in patients with multiple lacunar infarctions.[44] Cough reflex and spontaneous cough are also suppressed during sleep in patients with evidence of cerebrovascular damage.[2] Hence patients with cerebrovascular disease are particularly susceptible to the development of aspiration pneumonia during sleep. Other evidence exhibiting the importance of cerebrovascular disease comes from studies of patients with silent cerebral infarction, that is, patients with radiographic evidence of infarction without frank signs of neurological impairment. Silent cerebral infarction is fairly common among the elderly. Silent cerebral infarction was observed in 23% of elderly people in the USA, in 42% of older adults in one Japanese study and in 51% in another Japanese study.[2] Not only is silent stroke a risk factor for clinical stroke that obviously increases the risk of aspiration pneumonia, but Nakagawa *et al*. reported that patients with silent cerebral infarction were more likely to develop pneumonia (20%) than were controls (5%) without silent cerebral infarction over a 2 year period.[45] In this study, deep silent infarcts were more closely associated with the incidence of pneumonia (29%) than that in superficial infarcts (7%).[45] Hence silent cerebral infarction should be considered as a potential risk for the development of aspiration pneumonia. Taken together, it is reasonable to propose that treatment aimed at reducing the incidence and severity of cerebrovascular diseases, for example, antihypertensive therapy or anticoagulation and anti-platelet therapy in selected populations, may not only prevent future stroke but also reduce the incidence of aspiration pneumonia. In a comparison between a group receiving cilostazol, an anti-platelet agent, for 3 years and a cilostazol non-receiving group, the incidence of cerebral infarction decreased to 50% in the cilostazol group.[2] Furthermore, the incidence rate of pneumonia also decreased by approximately half.

Folic acid

Folate plays a pivotal role in the synthesis of dopamine and its deficiency is common in older people, especially in institutionalized subjects. Folate deficiency may be an independent marker for increased risk of aspiration pneumonia in older people.[46] Folic acid supplementation may prevent the incidence of pneumonia by improving the swallowing function in these susceptible subjects.[46] Therefore, for older people, in order to prevent pneumonia, nutrition also has to be taken into consideration.

Menthol

Ebihara *et al*. found that menthol stimulation and also cold stimulation restore impaired swallowing reflex in patients with dysphagia through the activation of transient receptor potential (TRP) M8.[47] Thus, an addition of menthol to liquids or food may improve swallowing reflex and help to prevent aspiration pneumonia in the elderly with dysphagia.

Banxia houpu tang

Iwasaki and co-workers reported that a traditional Chinese herbal medicine, banxia houpu tang (BHT), improves both swallowing and cough reflexes in patients with stroke.[48,49] Furthermore, they reported that treatment with BHT reduces the risk of pneumonia and pneumonia-related

mortality in elderly patients with neurodegenerative disorders.[50]

Black pepper oil

Ebihara *et al*. reported that olfactory stimulation by nasal inhalation of volatile black pepper oil (BPO) increases the cerebral blood flow of the right orbito-frontal and left insular cortexes, increases serum levels of substance P and improves swallowing function.[51] Inhalation of BPO might improve swallowing movement and might have benefits in older post-stroke patients with dysphagia, regardless of their consciousness level or physical and mental status.

Mosapride

Percutaneous endoscopic gastrostomy (PEG) is widely used for gastrointestinal tract access to provide artificial feeding in patients with neurological dysphagia. PEG tube placement is frequently requested to address problems of dysphagia with aspiration pneumonia. However, pneumonia is the most common cause of death and might explain the lack of survival benefit in patients fed using a PEG tube. A quantitative scintigraphic study with Tc-99m-labelled enteral infusion demonstrated frequent episodes of gastroesophageal reflux (GER) and subsequent aspiration of gastric contents into the airway in patients with gastrostomy.[52] Mosapride citrate is a gastroprokinetic agent that enhances upper gastrointestinal motility and is known to prevent GER in patients with GER disease. He *et al*. found that mosapride citrate lowers the rate of developing pneumonia after PEG and improves the survival rate in patients with PEG.[53]

Oral hygiene

The microbiological aetiology of aspiration pneumonia is usually traced to organisms that inhabit the oropharynx and aspiration of pharyngeal contents has been suggested as the mechanism by which these bacteria reach the lower respiratory tract.[2] Johanson and Harris speculated that the pulmonary infections caused by bacteria following the introduction of pathogenic organisms by aspiration of oropharyngeal contents is one of the major reasons for pneumonia in the elderly.[54] Since aspiration of bacteria in the oropharyngeal secretions is an important risk factor for nosocomial pneumonia in the elderly, poor oral health may also contribute to the development of pneumonia. Yoneyama *et al*. assessed the rate of pneumonia in elderly people receiving oral care and in those who were not.[55] During 2 years of follow-up, pneumonia was diagnosed in 19% of the participants who did not receive oral care and in 11% of those who received it. The relative risk of developing pneumonia in no active oral care compared with that in oral care was 1.67 (95% CI, 1.01–2.75; $p < 0.05$). Thus, monitoring the attention given to the oral hygiene of dependent patients can probably lower the incidence of aspiration pneumonia. Furthermore, Yoshino *et al*. stimulated the gum-ridge with a brush without toothpaste immediately after a meal.[56] No matter where in their mouth they stimulated, the swallowing reflex improved after the stimulation on the gum-ridge. This result indicates that stimulation in the mouth is transmitted to the brain and certainly improves the swallowing reflex, which is one of the most important defensive reflexes against microorganisms with which the human body is equipped. Brushing in the mouth is not only good for the prevention of dental caries and gumboils but also very good for improving the reflexes. Stimulation of the mouth requires less time and effort than stimulation of the arms and legs. All we need is a small amount of stimulus to care for older people.

Sitting position

GER is very common in general and more common in elderly subjects. It has been estimated that more than one-third of older people have intermittent symptoms of GER. In addition, the supine position, possibly by increasing the likelihood of aspiration of gastric contents into the lung, may lead to pneumonia in patients on mechanical ventilators.[2] Finally, nasogastric tubes promote aspiration of gastric contents by impairing swallowing function, causing stagnation of oropharyngeal secretions and reducing the tone of the lower oesophageal sphincter.[2] The simple approach to all of these problems may involve elevating the position of the bed. Meguro *et al*. showed that elevating the bed after each meal for 2 h may lower the febrile days presumptively caused by aspiration of gastric contents.[57] Matsui *et al*. also emphasized the importance of a patient's sitting position for the prevention of respiratory tract infections.[58]

Avoid neuroleptics

The cough reflex can, of course, be suppressed by sedative drugs. Irwin *et al*. reported a consensus panel report of the American College of Chest Physicians, 'Managing Cough as a Defense Mechanism and as a Symptom,' and did not identify any age-related changes in cough reflex.[59] However, depression of cough reflex by anaesthesia, sedative hypnotics or analgesic narcotics should be considered to be a major risk for aspiration pneumonia in older patients, especially during sleep. Attention to minimizing the use of agents that suppress the cough reflex is crucial in caring for elderly patients. When older people take benzodiazepines, their swallowing reflex will not decrease significantly. However, when they take neuroleptics, which mostly act as a dopamine receptor antagonist, their swallowing reflex clearly does decrease, which makes things even more troublesome and leads to pneumonia.[60]

Handwashing

Gram-negative bacilli and *Staphylococcus aureus* commonly colonize the hands of healthcare providers. Although usually transient, hand colonization may persist, particularly in workers with dermatitis. Handwashing before and after contact with patients is an effective method for removing transient bacteria,[2] but this is often a neglected behaviour by medical personnel. The use of gloves and gowns can significantly reduce nosocomial infection and pneumonia. Hospitals with effective surveillance and infection control programmes have rates of pneumonia 20% lower than hospitals without such programmes. Adherence to infection control practices such as handwashing is fundamental for the prevention of nosocomial pneumonia. Unfortunately, such barrier methods will not be effective in preventing infection with organisms that are part of the critically ill patient's endogenous flora; hence most Gram-negative pneumonias cannot be avoided by isolation methods.[61] Improved handwashing practices and appropriate handling of mechanical feeding, suction and respiratory devices should reduce the spread of infectious agents in institutional settings.

Prevention of pneumonia among the elderly by vaccines

Influenza vaccines

Influenza vaccination is effective in older adults in preventing not only primary influenza pneumonia but also secondary bacterial pneumonia. Although an increased risk of pneumonia mortality is found in patients with limitations in activities of daily living, even bedridden elderly patients can be effectively immunized against influenza and the duration of febrile days and all respiratory conditions associated with influenza can be reduced.[62]

23-Valent pneumococcal vaccines

The efficacy of pneumococcal vaccine among high-risk patients has been the subject of some controversy. Some investigators estimate an ~60–95% prevention rate of pneumonia by 23-valent pneumococcal vaccine in immunocompetent elderly and in other high-risk patients.[63] It is currently recommended in the USA that all adults aged 65 years or older and those at risk because of underlying illnesses receive both of these vaccines. Chiba *et al*. demonstrated that pneumococcal vaccination significantly shortened the overall febrile days and significantly reduced the rate of hospitalization for pneumonia even in bedridden patients.[64] Pneumococcal vaccination is of benefit and recommended for elderly disabled patients at high risk for pneumonia.

Bacillus Calmette–Guérin (BCG) vaccines

The tuberculin skin test is an easy way to check the cell-mediated immunity in elderly people.[65] Almost all Japanese people over 65 years old may have a positive tuberculin skin test. If a person shows negative, it means that his or her cell-mediated immunity is depressed. We undertook a trial to vaccinate bedridden elderly people with BCG vaccine. During follow-up, new pneumonia was diagnosed in 42% of the elderly disabled patients with negative tuberculin responses, in 15% of the tuberculin converted patients by BCG and in 13% of the patients with positive tuberculin responses. BCG inoculation might reactivate the depressed T helper-1 mediated cellular immunity and prevent pneumonia in immobile elderly patients.[66]

Conclusion

Silent aspiration, which is frequently observed in patients with basal ganglia infarctions, might be an important risk factor for pneumonia in elderly patients. Measurement of a swallowing latency is useful for identifying a subject susceptible to pneumonia. The swallowing function might be partly regulated by dopaminergic neurons and substance P-containing sensory nerves. Disruption of the basal ganglia leads to an impairment of the swallowing function and may predispose stroke patients to pneumonia. ACE inhibitors and amantadine may have beneficial effects for the prevention of pneumonia. Similarly, oral care improves swallowing reflexes and lowers the risk of pneumonia. Vaccines are also effective even in disabled elderly patients in a bedridden condition. Since pneumonia in elderly patients frequently recurs and is often lethal, it is important to identify and protect high-risk patients from pneumonia.

Key points

- The main theme is to discuss how aspiration pneumonia develops in older people and to suggest preventive strategies that may reduce the incidence of pneumonia among older adults.
- Silent aspiration of oropharyngeal bacterial pathogens to the lower respiratory tract is one of the most important risk factors for elderly pneumonia. Impairments in swallowing and cough reflexes among older adults, for example, related to cerebral basal ganglia infarctions, increase the risk of pneumonia.
- Since both swallowing and cough reflexes are mediated by endogenous substance P contained in the vagal and glossopharyngeal nerves, pharmacological therapy using ACE inhibitors,

which decrease substance P catabolism, can improve both reflexes and result in the lowering of the risk for pneumonia.

- Since the production of substance P is regulated by dopaminergic neurons in the cerebral basal ganglia, treatment with dopamine analogues or potentiating drugs such as amantadine can reduce the incidence of pneumonia.

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CHAPTER 49

Interstitial lung disease and lung cancer

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Interstitial lung disease

Background and epidemiology

Interstitial lung disease (ILD) refers to a range of pathologies that stimulate an inflammation or fibrosis of the lung interstitium, which comprises the connective tissues of the alveolar and bronchial epithelium and its surrounding vascular and lymphatic tissues. If the interstitium is damaged, efficient gas exchange will not occur.

There is a wide range of conditions that make up the ILDs (Table 49.1), only a few of which can be discussed in this chapter. Many of these increase in prevalence with advancing age. The most common conditions in older adults are idiopathic pulmonary fibrosis (also known as cryptogenic fibrosing alveolitis), hypersensitivity pneumonitis and the pneumoconioses. Although most ILDs increase their prevalence with age, sarcoidosis and chronic eosinophilic pneumonia appear to be less common with advancing age. There is a paucity of research on the interaction of age and ILDs, hence much of the investigation and treatment strategies are similar for adults of any age except that perhaps bronchoscopies and lung biopsies are less frequently undertaken.

Any patient presenting with respiratory symptoms, especially chronic cough and breathlessness, should have a detailed history taken of occupation, pets (especially birds), hobbies and smoking history. In general, all patients suspected of these conditions should be referred to a respiratory physician for assessment and treatment.

Main clinical features

Most patients present with insidious onset breathlessness, although some will present with a dry cough. Wheeze is uncommon as it usually represents larger airway narrowing. The rapidity of symptom progression may vary markedly.

In severe cases, cyanosis may be present. Findings on examination may be minimal, but clubbing can occur in advanced disease and 'Velcro' crackles may be auscultated in both lung bases in around one-quarter of cases. There may also be signs to suggest an underlying connective tissue disease, such as scleroderma.

Investigations are similar for all such disorders. Pulmonary function tests typically reveal a restrictive disorder for most ILDs such that the FEV_1 is relatively less impaired than the FVC and so the FEV_1/FVC ratio is normal or high. The transfer factor of the lungs for carbon monoxide (TLCO) is reduced, as is total lung capacity (lung volume). Chest radiographs may sometimes be normal, but usually there are subtle features of increased nodularity, increased reticulation or reticulonodular changes. These are more likely to affect the periphery of the lung. The diaphragm and heart borders may appear less distinct or 'shaggy'. Pleural thickening with calcification may be associated with asbestosis. In most cases plain chest radiography is non-diagnostic and consequently most patients need a high-resolution (HR) computed tomographic (CT) scan. The HRCT scan can often determine the cause (especially for idiopathic pulmonary fibrosis), rendering bronchoalveolar lavage and trans-bronchial or open-lung biopsy largely unnecessary in this age group. Furthermore, the presence of co-morbidities or relatively advanced disease with poor lung function in very old patients at presentation may render biopsies risky.

Specific conditions

Idiopathic pulmonary fibrosis (IPF)

This is the commonest form of ILD in old age, with an incidence of five cases per 100 000 population.[1] The cause is unclear, but there are associations with cigarette smoking, gastroesophageal reflux and autoimmune disorders in some patients. Histologically the features seen are referred to as 'usual interstitial pneumonitis (UIP)' and this often

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Table 49.1 Range of conditions classified as interstitial lung diseases.

Idiopathic pulmonary fibrosis
Fibrosing alveolitis associated with autoimmune disorders
Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
Pneumoconioses
Cryptogenic organizing pneumonia
Wegener's granulomatosis
Drug-induced
Chronic eosinophilic pneumonia

has a distinct radiological appearance on HRCT scan of the thorax. Typically there is fibrotic change in both lungs, with a predilection for the bases and the periphery. Honeycombing of the lung indicates more advanced disease and fibrosis often pulls apart bronchioles, causing so-called 'traction bronchiectasis'.

In fact, IPF is only one type of the so-called 'idiopathic interstitial pneumonias'. Details are outside the scope of this brief review, but a common alternative diagnosis is 'non-specific interstitial pneumonia (NSIP)'. The presence of ground-glass opacification may be more indicative of NSIP, indicating a more cellular reaction and one which may have a higher chance of response to treatment.

Median survival is estimated to be only 3 years for IPF, hence this condition needs to be regarded as a serious one with profound consequences that require a full and frank discussion with the patient.[2] A fall from baseline of >10% in FVC or >15% in TLCO in the first 6–12 months identifies patients with a much higher mortality.[3] Most clinicians are aware of patients who appear to have a better prognosis, with relatively stable lung function over many years, but who may then subsequently deteriorate rapidly over months.[4] Patients with NSIP have a better prognosis than those with UIP. They may survive for up to 10 years depending on the degree of fibrosis present. Treatment consists of high-dose oral corticosteroids and immunosuppressant drugs such as azathioprine and *N*-acetylcysteine, but the evidence base is rather weak.[2] No medical therapy has been shown to improve survival in IPF. Oxygen for symptomatic relief is commonly used in those who are hypoxic or who desaturate on exercise. There appears to be a remarkably high incidence (80–90%) of gastroesophageal reflux in patients with IPF,[5] such that some experts argue for routine treatment with proton pump inhibitors, although clinical trials are lacking.

Hypersensitivity pneumonitis (extrinsic allergic alveolitis)

This refers to an immune-mediated reaction to organic particles, which may occur in susceptible individuals. The response is usually a chronic type 3 hypersensitivity reaction, but an acute type 1 reaction may occur, presenting as acute breathlessness, cough and even fever. Numerous antigens are known to trigger such reactions, but two are particularly common in older adults. Chronic exposure to avian proteins can lead to 'bird fancier's lung' and fungal spores (such as actinomycetes) found in mouldy hay can cause 'farmer's lung'. Because exposure to such antigens may not be obvious, a careful history should be taken, including inquiring about pets, pastimes and occupation. Chest radiography and CT scan may reveal micronodular changes or a ground-glass appearance in the mid and lower zones, progressing to established fibrosis with honeycombing and volume loss in more chronic cases.

Antigen testing can be undertaken to prove exposure, while pulmonary function tests demonstrate restrictive features and volume loss. Management consists of avoiding further exposure to the antigen, although this may not always slow the deterioration of the condition. In common with other physicians, the present author has encountered many patients who are, perhaps understandably, somewhat averse to the thought of being parted from their pet budgerigar! In such cases, asking someone else to clean out the bird's cage could be suggested. Oral corticosteroids may help alleviate symptoms, especially in the acute or subacute stages where a cellular response is still occurring.

Pneumoconioses

This refers to fibrosis or damage to the lung due to inorganic dust. The most common causes are asbestosis, coal dust and silicosis. Coal workers' pneumoconiosis is now rarely seen in the Western world *de novo*, although chronic cases may be encountered in older people. Coal dust causes a combination of fibrosis and centrilobular emphysema (the fibrosis pulling apart the alveolar spaces), occasionally leading to progression even after dust exposure has ended. Progressive massive fibrosis, usually in the upper lobes, is reported but rarely encountered nowadays.

Silicosis is similarly fairly rare in the Western world, but is still common in some developing countries, especially those with a major mining industry. Silicosis may occur due to exposure to common rock dusts (e.g. granite and sandstone) as a result of quarrying, foundry work or mining. Small particles of silica may be inhaled distally into the lungs and ingested by alveolar macrophages which become activated, releasing inflammatory mediators such as cytokines and interleukins which may damage the respiratory cell structure and its interstitial matrix.

Although there is an acute form, symptoms are usually of progressive dyspnoea or symptoms suggestive of chronic obstructive pulmonary disease (COPD) and may occur several years after silica exposure. Radiologically small (<10 mm) nodules may be seen diffusely in the lung, although with an upper lobe predominance. 'Eggshell calcification' of hilar lymph nodes is rather rarely seen. Patients

with silicosis are at increased risk of lung cancer and also tuberculosis, probably due to damage to pulmonary macrophages by particles of silica. Progressive massive fibrosis may occur in severe cases, with lung cavitation.

Asbestosis refers to parenchymal fibrosis in those who have had considerable exposure to asbestos usually many years before the disease is manifest. Bilateral lower zone infiltrates may be seen radiographically and the condition often progresses after exposure has ended. The presence of pleural plaques may also suggest the diagnosis, although this is an entirely separate entity and other conditions, such as COPD, may coexist, confounding the diagnosis.

There is no specific treatment for these conditions, being essentially supportive. In certain countries, compensation may be claimed for industrial exposure.

Lung cancer

Background and epidemiology

The epidemic of lung cancer, apart from mesothelioma, is gradually improving in most Western countries but rates are still increasing in many other parts of the world. Approximately 90% of cases of lung cancer are attributable to tobacco exposure and historical smoking patterns explain this variance. Most recent data from the UK indicate that only 12% of those aged over 65 years of age are current smokers.[6] Mortality rates have declined steeply for all age groups, beginning first with younger men in the 1960s and last for the over 85-year-olds in the late 1980s.[6] For women, this fall began rather later as smoking uptake occurred in a later cohort compared with men. Across the world, countries are at different stages in their lung cancer epidemic due to differing histories of tobacco consumption, hence the rates of lung cancer vary widely. Worldwide it is estimated that 1.4 million people died of lung cancer in 2008.[6]

The majority of lung cancer still occurs in older people, with the incidence reaching a peak at around 75 years of age. This is because approximately 15 years separates initial cellular mutation from clinical presentation and as cells age there is a greater risk that DNA repair mechanisms may be impaired, leading to cancerous transformation.

Long-term cancer mortality rates are still higher in older adults than younger people.[7] Although historical data strongly suggest that lung cancer in old age is poorly assessed and treated,[8] more recent information in this regard is lacking.

Patients with lung cancer of any type should nowadays be referred to and managed by a specialist multidisciplinary team. This usually comprises a respiratory physician, nurse specialist, oncologist, radiologist and pathologist, with strong links to palliative care specialists. Despite this, the 5 year survival rate for all ages is still disappointingly low, at around 7% (2003–2007 UK data[6]).

Main clinical features

Most patients present with similar symptoms whatever their age, including cough, breathlessness, haemoptysis and weight loss. Unfortunately, the condition still tends to be diagnosed at a more advanced stage in older adults than young subjects and it may be complicated by multiple pathology.[9]

The extent of the disease at diagnosis, the functional and cognitive status of the patient and their own wishes for further investigation are even more important in people of advanced age. Care needs to be taken to ensure that important survival benefits and potential improvements in quality of life are not missed due to therapeutic nihilism. For many patients, complete cure is not possible but a more active approach can prove beneficial.

After a history and basic laboratory tests, spirometry should be performed to ascertain baseline lung function. There is little place for sputum cytology as most patients undergo bronchoscopy if a central lesion is identified or CT scan with CT-guided biopsy if feasible for a peripheral lesion. If there is no evidence of metastatic disease, the presence of mediastinal lymph node enlargement is critical in determining whether surgery is an option. This can be clarified using positron emission tomography (PET) scanning, which can also detect extra-thoracic spread. If nodal involvement is suspected, then endo- or trans-bronchial ultrasound-guided needle aspiration can be considered.[10]

Specific conditions

Lung cancer is broadly classified into three types:

1. non-small cell cancer (NSCLC)
2. small cell lung cancer (SCLC)
3. pleural mesothelioma.

Other types of tumour may be occasionally seen, such as carcinoid, but these will not be discussed further here.

Non-small cell lung cancer

NSCLC consists of several types of tumour. They are often grouped together because they have the potential for cure through surgical resection. Squamous cell (or epidermoid) carcinoma is the most common lung cancer among older adults, accounting for up to half of cases in this age group. These tumours often grow slowly and usually arise in central airways. Adenocarcinoma, bronchoalveolar cell carcinoma and large cell carcinoma together make up around one-quarter of cases. Adenocarcinomas arise from bronchial and mucosal glands and, unless identified at an early stage, generally have a worse prognosis than squamous cell carcinoma.

At diagnosis, patients can be divided into those in whom surgical intervention is an option (stages 1 and 2 mainly) and those whose disease is too extensive (stages

3 and 4) or those who are not fit for surgery. Successful surgery will depend particularly on the absence of mediastinal lymph node involvement. It is not possible to discuss the intricacies of lung cancer staging further in this brief review.

A full assessment for surgery should take into account lung function, performance status and comorbidities, and also patient wishes. For older adults, whether there has been a substantial shift in clinical practice towards greater intervention in the last few years is uncertain. There is a paucity of clinical trial data in this age group. However, the development of specialist multidisciplinary lung cancer teams in the UK has led to a more detailed evaluation of such cases in the present author's experience. Most data suggesting a lack of investigation in older adults are over 10 years old, but this does not necessarily mean that interventions are more aggressive. Studies suggest that age *per se* is not an independent prognostic indicator in lung cancer. In terms of survival, a recent overview of several trials considered that patients aged 70 years or more undergoing lung resection responded as well as younger patients in terms of morbidity, mortality and quality of life.[11] The authors found no significant difference in 5 year survival rates following surgery for stage I disease (<70 years, 69–77%; >70 years, 59–78%), although older patients received higher rates of palliative care. In a study of octogenarians undergoing curative lobectomy, the perioperative death rate was 3.7% and the survival rates for patients with stage I disease were 86% at 1 year and 62% at 3 years.[12] For pneumonectomy, perioperative mortality rates for patients aged over 70 years were high in one centre (17%), indicating that great care with patient selection is vital.[13]

Selection for surgery in older adults needs to take account of cardiac and pulmonary status, particularly the presence of significant COPD. Calculating the likely lung function status after surgery is necessary: a predicted postoperative FEV_1 >40% is usually recommended.

NSCLC is generally not very sensitive to chemotherapy, although third-generation single-agent chemotherapy is considered the standard of care for patients with advanced/metastatic disease. A study in older age groups showed that the median survival may be increased from a median of 21 weeks to 27 weeks with chemotherapy, although side effects are slightly more common.[14] Such studies may also suffer from selection bias in that only those patients judged fit enough for chemotherapy might be put forward for inclusion.[15] Prospective studies in this age group are urgently needed. There have been similarly few older adult specific trials of radiotherapy in lung cancer and current treatment is often based on evidence extrapolated from studies treating younger patients. Radiotherapy is usually used for palliation of symptoms such as haemoptysis and chest wall or bony pain and appears well tolerated.[16]

Small cell lung cancer

SCLC accounts for ~15–20% of lung cancers and, as a proportion, is slightly more common in older adults than younger age groups. Small cell tumours invade the submucosa early in their growth and patients usually present with regional or distant metastases at diagnosis. As it is a rapidly growing tumour, it is the most chemo-sensitive of all the lung cancers. The standard treatment for limited-stage disease is platinum-based chemotherapy, combined with radiotherapy, whereas chemotherapy alone is used for extensive-stage disease. Drugs also include etoposide, which is oral and easily administered on an outpatient basis. In the older adult, there are limited prospective data available to guide treatment decisions, but the existing data demonstrate that standard approaches are feasible in older adults who have been thoroughly assessed and informed.[17] Untreated, the median survival for small cell cancer is only 4 months, but chemotherapy can add several months of life which is generally of good quality.[17]

Pleural mesothelioma

Mesothelioma principally affects the pleural lining, although it can affect the peritoneum or rarely the pericardium. It is almost always caused by past exposure to asbestos dust, notably blue asbestos, usually as a hazard of occupation. There is no association with smoking. Due to the long latent period of between 30 and 50 years (and rarely 15–60 years) between exposure and symptoms, peak incidence is found in patients about 70 years old. Death rates for all ages are expected to peak by 2015–2018 in Europe. Whereas the rate is decreasing in younger age groups, it has continued to increase in older age groups, especially those born around 1940.[18] Chest wall pain, breathlessness and weight loss are the commonest presenting symptoms. A chest radiograph may reveal pleural thickening or a pleural effusion. Examination of tapped pleural fluid is diagnostic in relatively few cases. A CT scan of the chest may be highly suggestive and further thoracoscopy may be required to obtain histology, if the patient's condition permits.

In most cases, the prognosis is poor, with a median of 9 months, and treatment modalities are still disappointing. Chemotherapy with pemetrexed and carbocisteine has been shown to improve the survival to a median of 13 months.[19] Those aged over 70 years appear to do as well as those under 70 years, except for some mildly increased haematological toxicity, although regrettably few patients have been studied over the age of 75 years.[20] Multimodality treatment including surgery, radiotherapy and chemotherapy has also been studied. Surgery followed by aggressive chemotherapy may increase the prognosis to around 3 years. Surgery usually involves either extrapleural pneumonectomy or pleurectomy/decortication. These

options will depend on tumour type and how locally advanced the cancer is.[21]

High-quality palliative care is crucial, as with all cancers, including the control of symptoms such as breathlessness and chest wall pain and the many other associated features. Pain in the chest wall is often due to invading tumour and may require opiates, non-steroidals, neuropathic medication or nerve blocks. Counselling is important to support patients and their families, in addition to exploring issues around advanced care planning. The condition is a recognized industrial disease and patients are entitled to claim for compensation.

Key points

- Interstitial lung disease includes idiopathic pulmonary fibrosis, hypersensitivity pneumonitis (extrinsic allergic alveolitis) and pneumoconioses.
- Lung cancer includes non-small cell and small cell lung cancer and pleural mesothelioma.
- Chemotherapy of the various conditions is discussed.
- Most interstitial lung diseases (ILDs) increase in prevalence with age.
- A detailed history, pulmonary function tests and high resolution CT scans will clarify the cause in the majority of cases of ILD.
- The prevalence of lung cancer is falling but most cases are still diagnosed at an advanced stage in older people.
- Older patients with suspected lung cancer should be referred to a specialist team for active investigation.

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CHAPTER 50

Chronic obstructive pulmonary disease and asthma

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Chronic obstructive pulmonary disease (COPD)

Epidemiology

The hallmark of COPD is the presence of airflow obstruction that is not fully reversible and which demonstrates little variability over time. It is usually progressive and there may be a range of pathological changes in the lung, including small airways disease and emphysema. The airflow obstruction in COPD is usually insidious in onset and progresses over a number of years or decades. As the airflow obstruction worsens, the risk of complications and exacerbations increases, impairing quality of life.

COPD is the fifth largest cause of disability in the world and is the fourth leading cause of death in the USA. A worldwide prevalence of 10.1% has been estimated, higher in Western countries which have older populations with greater lifetime exposure to tobacco.[1] Despite this, it is known that COPD is underdiagnosed and misdiagnosed, especially in older adults. Based on smoking patterns it is likely that between half and two-thirds of patients with COPD are unknown to their health provider.[2] Older adults may regard breathlessness as part of the ageing process and not seek medical attention. Comorbid conditions, social isolation, depression and a reduction in the perception of breathlessness may also have a role. Furthermore, there may also be a lack of diagnostic equipment such as spirometry in primary care, leading to mislabelling.

COPD is usually caused by cigarette smoking, although passive smoke exposure may also contribute. The Forced Expiratory Volume in 1 second (FEV_1) declines by about 25–30 ml per year after the age of 25 years in healthy adults, but in susceptible smokers that decline exceeds 50 ml per year. COPD is associated with significant comorbidities.

Diagnosis and clinical features

The diagnosis of COPD relies on clinical judgement and the presence of airflow obstruction. The precise definition of airflow obstruction has been the subject of much academic discussion. International consensus guidelines [such as those of the Global Obstructive Lung Disease (GOLD) collaborative] support the diagnosis of airflow obstruction if, on spirometry, the FEV_1/FVC (forced vital capacity) ratio is <0.7 post-bronchodilator. Incorporating the need to assess the patient after bronchodilation reduces the potential for misdiagnosing a reversible lung disease such as asthma. The UK National Institute of Health and Clinical Excellence (NICE) also advises that if the FEV_1 is $\geq 80\%$ of the predicted value, then the diagnosis should only be made in the presence of respiratory symptoms. This is because, as the lung ages, FVC begins to decline later than FEV_1 and at a slower rate, which results in a natural fall in the FEV_1/FVC ratio from about 75 to 70% by 70 years of age.[3] Therefore, a definition which relies purely on the FEV_1/FVC ratio will be less discriminatory in very old people, who may receive an inappropriate label.

A diagnosis of COPD should be entertained in patients with a risk factor (usually smoking) and one or more symptoms of exertional breathlessness, wheeze, chronic cough, chronic sputum production and 'winter bronchitis'.[4] In its early stages, symptoms may be intermittent or limited to a cough productive of clear or white sputum. Patients may also present with wheeze or a 'chest infection' which fails to improve as rapidly as expected. Most patients with COPD have a history of at least 20 pack-years of smoking (one pack-year being the number of cigarettes smoked per day, divided by 20, multiplied by the number of years smoking).

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Clinical examination may reveal little in the early stages, although wheeze may be present. As the condition progresses over years and FEV_1 falls further, lung hyperinflation occurs and hypoxia may develop, being common in those with an FEV_1 <30%. More profound hypoxaemia (i.e. a PO_2 <8 kPa) leads to pulmonary hypertension and right-sided heart failure, often manifest as peripheral oedema, a raised jugular venous pressure and sometimes secondary polycythaemia.

The differential diagnosis of COPD is wide and the most significant features are summarized in Table 50.1. In older adults, comorbidities are common. COPD is a major risk factor for cardiovascular events, independent of smoking.[5] Heart failure is present in 20% of patients with COPD over 65 years of age.[6] Bronchiectasis has also been found on high-resolution computed tomography (CT) scan in up to 29% of patients with confirmed COPD and chronic bronchitis in primary care[7] and may manifest itself as a cause of frequent exacerbations. Osteoporosis is also more common in patients with COPD, partly due to the effects of corticosteroids.

Investigations

Spirometry is considered possible in ~85% of older adults, cognitive impairment being a major reason for inadequate results. Reversibility testing is not usually helpful, except where there may be doubt about a diagnosis of asthma (see later). A chest radiograph should be performed in all suspected new cases of COPD, mainly to exclude other conditions and to ensure that there is no evidence of lung cancer. If signs of cor pulmonale are present on examination, an ECG may show features of right-sided heart strain. Owing to the significant overlap with heart failure, echocardiography should be considered in those with relevant clinical features or a failure to respond to initial treatment. If doubt remains, more detailed tests of lung function can be undertaken, including transfer factor for carbon monoxide (T_LCO) and a CT scan of the thorax if symptoms seem disproportionate to the level of lung function or if abnormalities are seen on the chest radiograph.

Table 50.1 Differential diagnosis of COPD.

Condition	Features
Asthma	Non-smoker, symptoms likely to vary, nocturnal symptoms, reversibility of airflow obstruction
Congestive cardiac failure	History of ischaemic heart disease. Orthopnoea, bibasal crackles on auscultation, chest X-ray evidence of pulmonary oedema and cardiomegaly Restrictive pattern on spirometry
Bronchiectasis	Large-volume purulent sputum, coarse crackles basally, clubbing, airway thickening on chest radiograph
Interstitial lung disease	Dry cough, fine crackles basally, industrial exposure, drug toxicity Restrictive picture on spirometry Impaired lung diffusing capacity
Kyphoscoliosis	Characteristic skeletal abnormalities Paucity of findings on chest examination Restrictive picture on spirometry Normal lung diffusing capacity

Assessing COPD severity

There is a relatively poor association between lung function and health status. Nevertheless, the condition is still generally categorized into different levels of severity according to percent predicted FEV_1 (Table 50.2). Other important aspects to consider in the assessment of an older person with COPD are as follows:

- breathlessness (e.g. MRC dyspnoea scale)
- disability/health status (e.g. Manchester Respiratory ADL scale)
- exercise tolerance (e.g. shuttle walking test or 6 min walk)
- BMI
- oxygen saturations if FEV_1 is <50% or signs of cor pulmonale
- anxiety and depression [e.g. Hospital Anxiety and Depression Scale (HADS)]
- exacerbation rates.

Management of COPD – stable state

Stopping smoking has been shown to reduce significantly the age-related decline in FEV_1. It is vital that patients who continue to smoke are encouraged to stop and are

Table 50.2 International classification of severity of airflow obstruction.

Post-bronchodilator FEV_1/FVC	FEV_1 predicted (%)	Severity of airflow obstruction
<0.7	≥80	Stage 1 – mild
<0.7	50–79	Stage 2 – moderate
<0.7	30–49	Stage 3 – severe
<0.7	<30	Stage 4 – very severe

Source: American Thoracic Society/European Respiratory Society Guidelines 2004; GOLD Guidelines 2008; National Institute of Health and Clinical Excellence 2010.

supported throughout this process, with the help of appropriate therapies such as nicotine replacement therapy, bupropion or varenicline. Quit rates are as good if not better in older adults than in their younger counterparts. Pneumococcal and annual influenza vaccination should be offered to all patients.

COPD should be managed by a multidisciplinary team, many aspects of which are incorporated into pulmonary rehabilitation programme. Patients with more severe airflow obstruction may be considered for enrolment in a chronic disease management programme, with support at home by specialist nurses. The use of patient self-management plans is vital, including advice about recognizing and treating exacerbations. As the condition progresses, there should also be the opportunity to discuss advance planning and end-of-life care wishes.

Pharmacological management of stable COPD

Treatment is targeted at reducing breathlessness and limiting the sequelae of COPD, by impacting positively on health status and exacerbation rates. Over the past few years, it has been appreciated that preventing an exacerbation is of particular importance, due to its impact on lung function, health status and mortality. The GOLD guidelines suggest that frequent exacerbations should be considered present if there is one or more per year for the past 3 years, whereas NICE suggest two in the previous 12 months, and this should guide treatment decisions. Treatment options may seem complex but are simpler when displayed as an algorithm (Figure 50.1).

Breathlessness and wheeze are initially treated using a short-acting inhaled bronchodilator as required (either a β_2-agonist, e.g. salbutamol, and/or an antimuscarinic, e.g. ipratropium bromide). If patients with stage 2 disease ($FEV_1 \geq 50\%$) are still symptomatic or exacerbate frequently despite this, guidelines advise the regular use of a long-acting β_2-agonist (LABA) (e.g. salmeterol or formoterol) or a long-acting muscarinic antagonist (LAMA) (e.g. tiotropium). The latter is certainly more effective than regular ipratropium bromide. There is strong evidence that LABAs and LAMAs have a positive impact on symptoms, health status and exacerbation rates. Furthermore, tiotropium has been associated with a small reduction in all-cause mortality.[8]

In stage 3 disease ($FEV_1 < 50\%$), where a patient remains breathless or where there are repeated exacerbations, despite a LABA, then there are two main options. First, an inhaled corticosteroid (e.g. beclomethasone, budesonide, fluticasone) could be added to the LABA in a combination inhaler (e.g. Seretide, Symbicort). A Cochrane review has shown that this combination reduces exacerbations by 9% and mortality by about 20% compared with steroids alone in stable COPD.[9] Unfortunately, clinical trials have shown a small but significant increase in the risk of non-fatal pneumonia in patients receiving inhaled corticosteroids, but this does not outweigh the benefits of their use.[10] Second, a LAMA (currently tiotropium) may be added to an existing LABA.

In patients who remain breathless or who exacerbate frequently, regardless of FEV_1, a LAMA could be added in addition to an inhaled LABA–corticosteroid combination or vice versa.

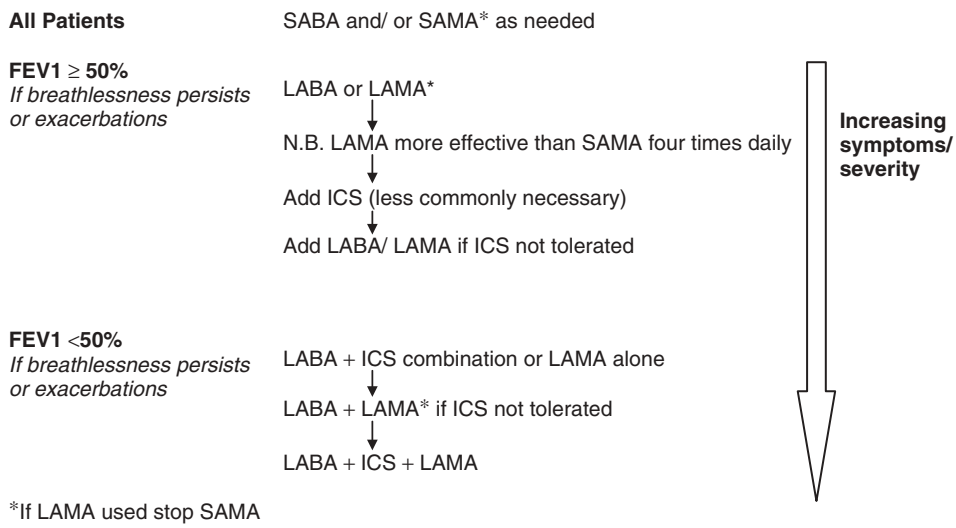

Figure 50.1 Inhaled medication in COPD. ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic agonist; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic agonist.

It is important to determine whether new treatments improve symptoms, exercise tolerance and ability to perform ADLs, rather than simply alter lung function, which is less relevant. If treatments are used primarily to minimize exacerbations, then they should be continued in a preventive capacity, whereas those given for symptom improvement could be discontinued if ineffective after a month's trial.

If symptoms persist or for patients unable to use inhalers correctly, a theophylline may be considered; slow-release preparations are preferred. Doses should generally be kept low in older people to avoid gastrointestinal side effects and the risk of drug interactions, particularly antibiotics during exacerbations. In addition, a trial of mucolytic therapy can be considered if sputum viscosity is increased. Nebulized bronchodilators may be of help for those patients with very advanced disease (who could be offered a symptomatic trial) or where the inhaler technique is so poor that no other relief is possible. In a few patients with advanced COPD, maintenance oral corticosteroids may be considered, but in general the risks outweigh the benefits.

Finally, it is important to recognize when a patient is in their last year of life so that they can be included in an end-of-life care register and offered appropriate palliation, including the use of opioids and benzodiazepines to ease symptoms of breathlessness that has failed to respond to medical therapy. All too frequently, the decision to move from an active to a palliative approach is made too late.

Long-term oxygen therapy (LTOT)

In severe COPD and in anyone with signs of cor pulmonale, referral for home oxygen should be considered. Short-burst therapy may improve symptoms of breathlessness if exercise desaturation is noted, and LTOT for at least 15 h per day has been shown to improve survival in patients with severe COPD and persistent hypoxaemia.[11] A simple screening test is to refer those with an oxygen saturation of <93%, or <95% and possible cor pulmonale. LTOT should be prescribed in a period of clinical stability to current non-smokers if the following conditions are met:

- PaO_2 <7.3 kPa, or
- PaO_2 7.3–8.0 kPa with evidence of secondary polycythaemia, pulmonary hypertension, peripheral oedema or nocturnal hypoxaemia.

Key questions remain concerning the benefit of oxygen therapy in improving quality of life and symptoms, issues which are especially pertinent to frail older patients. There remains a paucity of data regarding the benefits of LTOT in advanced old age, as randomized controlled trials have not been repeated in this group to date. The NOTT study did report improvements in polycythaemia and neuropsychiatric functioning.[11] Small improvements in cognitive function have been noted in a few studies, but these have generally been small and have not been in the oldest age groups. In some studies (mean age around 70 years), QOL and activities of daily living have not been shown to be better in those on LTOT,[12,13] but more recently a study did demonstrate small improvements in quality of life with LTOT after six months.[14] In the author's clinical practice, many patients do appear to derive symptomatic/qualitative benefit, but some do not. The addition to a patient's home of extra machinery and lengths of oxygen tubing may create a falls hazard. There may also be issues around safety in those with cognitive impairment or poor manual dexterity, although this has been poorly studied. Concerns such as these should be flagged up as experienced engineers will help with installation of switching mechanisms to divert the supply to individual rooms, reducing the risk of tripping. Logistical issues for patients on LTOT who reside in care homes must be considered, as should the training and support of care staff. Care home residents using concentrators overnight may need to have portable oxygen with conserver or free-standing cylinders if the day room facility is far from their bedroom.

Approximately 50% of patients receiving LTOT remain alive at 3 years.[15] Death tends to occur earlier in those with low BMI and comorbidities.[16] In older adults with COPD, the main factors predicting mortality are disability, low BMI, lung function and use of LTOT.[17]

Management of an exacerbation of COPD

Acute exacerbations of COPD are characterized by increased breathlessness, cough, increased sputum volume or purulence, wheeze and chest tightness. They account for up to 10% of all medical admissions to UK hospitals[18] and severe exacerbations are associated with an adverse effect on an individual's health status.[19] The outcome for patients admitted to hospital has probably improved slightly over the past few years, but about one-third are readmitted within 30 days and 15% have died at 3 months.[20] Exacerbations may be caused by viruses, bacteria or environmental pollutants, although in many cases the cause will remain unclear. The most common bacterial causes of exacerbations are *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis*.

Using antibiotics for exacerbations where there is increased cough and purulent sputum reduces mortality by 77% and decreases the risk of treatment failure by 53%.[21] A meta-analysis has shown that antibiotics reduce in-hospital mortality compared with placebo.[22] Local guidelines will determine the initial choice of antibiotic therapy, but amoxicillin or doxycycline are commonly used. It is reasonable, however, to withhold antibiotics if there is no sputum purulence and only one of increased

sputum volume or breathlessness.[23] There is a small but definite risk in giving too much oxygen to a patient with longstanding CO_2 retention (depressing the hypoxic drive and worsening acidosis), hence target saturations of 88–92% are advised.

Initial management with oral corticosteroids has been shown to reduce length of hospital stay and treatment failure compared with placebo[24] and so should be offered as standard. Treatment should be continued for 7–14 days depending on severity. For those using frequent courses of corticosteroids, prevention of osteoporosis should be considered.

For admitted patients, non-invasive ventilation (NIV) is considered in those with pH <7.35 despite maximum medical therapy. Compared with standard treatment, NIV reduces mortality, need for intubation and length of stay compared with standard therapy.[21]

Many hospitals have early supported discharge teams specifically for patients with COPD; some also provide an admission avoidance service. These have been shown to have similar clinical outcomes but also reduce length of stay and cost. Such services will provide daily patient review at home, with oxygen, nebulizers and medication as appropriate. Patient selection is crucial, especially in the older adult where a full assessment of functional and social situation is required. Typically, patients without acidosis and where there is good social support are suitable.

Asthma

Epidemiology

Asthma is a chronic inflammatory disorder associated with bronchial hyper-responsiveness and variable airways obstruction. It usually causes episodic symptoms of wheezing, cough, chest tightness and dyspnoea. The airflow obstruction may be fully or partially reversible either spontaneously or with treatment. Laennec (1781–1826), who invented the stethoscope, is believed to have provided the first case report of asthma in old age, occurring in an 82-year-old man who had had attacks of breathlessness for the previous 30 years. Yet until the late 1970s, it was generally thought that asthma in older people was rare. Several studies have since refuted this and have revealed an underdiagnosis of asthma in this age group. A cross-sectional survey of 6000 people aged 65 years and over in the UK was conducted with pulmonary function testing and found a prevalence of known asthma of 1.1%, and a further 2.4% of men and 1.2% of women had definite untreated asthma.[25] Most of these subjects were found to have moderate or severe disease. Untreated asthma was most common in individuals who actually had current symptoms of breathlessness or wheeze. Elsewhere, a prevalence of around 5% probable current asthma has been reported, with one study reporting that 39% of such patients were not taking any respiratory medication.[26] Reasons for underdiagnosis are likely to include under-reporting, activity limitation, social isolation, depression and a misconception that asthma is rare.

That the condition can be severe in older adults is certain. Hospital admission rates are higher for this age group than any other. A recent US review of epidemiological literature highlighted the fact that 50% of asthma deaths occur in people aged 65 years or over and that mortality may still be rising in this group.[27] The reasons for this are not clear, but the mode of presentation may be different, the risk of misdiagnosis higher, comorbidities are more common and undertreatment is more likely.[26]

About half of all older people with asthma will have noted their initial symptoms after the age of 40 years and 20% after the age of 60 years.[28] Asthma can start for the first time at any age and one US study found that the age- and gender-adjusted incidence was 103/100 000 in residents aged 65–74 years, 81/100 000 in those aged 75–84 years and 58/100 000 in residents older than 85 years.[29] This is not far below the incidence for younger age groups. There is some evidence to suggest that patients with longstanding asthma have more severe airflow obstruction than patients with more recent onset disease, but that in those with recent onset disease the subsequent decline in lung function may be worse.[30]

The cause of asthma at any age is still not clear. There may be host factors such as genetic susceptibility, atopy and obesity and environmental factors such as possible viral infections, pollution and occupational triggers. However, most research has been conducted in children and very little in older adults. In contrast to younger adults, asthma in old age is rarely associated with atopy, although there are cases where it does occur.[31] However, there is still a weak correlation with serum immunoglobulin E (IgE), lung function and bronchial hyper-responsiveness in older asthmatics, even though IgE levels do fall with advancing age. Most asthma in old age is regarded as 'intrinsic' and is more likely to start in adult life rather than in childhood. In this latter group, dysregulation of autonomic airway smooth muscle and changes in β-adrenoceptor activity have been reported.[32,33] Inflammation is still considered to be a central feature of 'intrinsic' asthma, involving eosinophils, T cells and specific cytokines such as interleukin-4. The result is airway smooth muscle contraction and oedema, mucus secretion and, if inadequately treated, airway remodelling. There is recent evidence for this in undertreated middle-aged people with asthma whose lung function declined faster than those on regular anti-inflammatory medication.[34] Ultimately, this could lead to irreversible disease and the phenotypic appearance of COPD, characterized by airflow obstruction that does not vary markedly over time.

Clinical features and diagnosis

There is no gold standard for the diagnosis of asthma. A good clinical history is paramount, followed by simple investigations and trials of treatment as necessary. Typical presenting features of asthma in all age groups include intermittent cough, particularly at night, shortness of breath, wheezing, chest tightness, sputum production and reduced exercise tolerance. These may be associated with viral or environmental triggers, exercise and emotions. Significant diurnal variation may be present in many cases, but in some the symptoms may be more persistent. The BTS/SIGN guidelines[35] recommend determining the probability of asthma, based on a number of factors, but in older adults these are less clear cut. There may be diagnostic confusion with other conditions such as COPD and heart failure. Older adults have less perception of bronchoconstriction and may also have a poorer appreciation of the severity of their disease.[36] Bronchial irritability symptoms such as cough and wheeze on exposure to conditions such as fumes and cold air are less commonly reported. Probing for signs of symptom variability is important, as it is an important distinction from COPD, which exhibits (predominantly) fixed airflow obstruction. However, the two conditions may also coexist, such as in a patient with asthma who smokes.[37] A thorough physical examination is important to exclude other diagnoses and in asthma may reveal wheeze or hyperinflation, but could be entirely normal.

Investigations should include a chest radiograph and spirometry. In patients without airflow obstruction (FEV_1/FVC ratio >0.7) the differential diagnosis would include gastro-oesophageal reflux, rhinitis, chronic cough and hyperventilation syndromes. It is always wise to check that there is not an underlying restrictive disorder such as pulmonary fibrosis (the FEV_1/FVC ratio will usually be normal or high and there may be chest signs). If asthma is still suspected, peak expiratory flow (PEF) monitoring can be undertaken for perhaps a two-week period. Most older adults, unless very frail, should be able to keep a reasonable record; indeed, they may be more meticulous than younger people. However, the greater the airflow obstruction the greater is the relative degree of PEF variability, and PEF variability itself also appears to increase with age. Records should be kept at least morning and night with the percentage difference between the mean morning result and the best results (of three attempts) obtained indicating the diurnal variation. A 20% change is suggestive of asthma and this can then be followed by trials of treatment to see whether the variation improves.

For patients with airflow obstruction the key is to determine whether this is fixed and varies little over time (COPD) or whether it is wholly or partially reversible. Older patients with chronic asthma tend to have only partially reversible airflow, probably as a result of damage to the airways due to unrecognized inflammation as discussed above. Where the differential diagnosis includes COPD or where COPD could be a comorbidity (e.g. in a former heavy smoker), then reversibility testing should be tried. A >400 ml improvement in FEV_1 following a β_2-agonist or a two-week trial of corticosteroids is generally considered strong evidence for asthma. Smaller improvements can occur in COPD patients and in some cases it may not be possible to differentiate the two conditions fully. Use of more discriminatory tests such as static lung volumes and T_LCO may be useful in such cases. A rise in total lung capacity is rare in asthma but is typical of more severe COPD. A decreased T_LCO indicates a loss of the alveolar-capillary surface which may be seen in emphysema (COPD) and not asthma. Where the result is equivocal, a trial of inhaled or oral corticosteroids may be conducted with PEF monitoring.

Management

The goals of asthma treatment in older adults are as follows:

1. to minimize or eliminate symptoms and maintain control
2. to improve quality of life and maximize activity levels
3. to prevent exacerbations
4. to treat the underlying inflammation, thereby reducing the risk of developing irreversible airflow obstruction.

Guidelines emphasize the need for 'zero tolerance' of any symptoms, such as night-time waking or cough. This approach has not been tested in the older age group where symptoms may be more chronic and stubborn.

Although treatment for older adults is influenced by the severity of symptoms, the fact that older adults may have a lower perception of bronchoconstriction should also be kept in mind. Hence they may notice symptoms later than younger adults, possibly leading to a delayed recognition of an exacerbation of airway obstruction. Therefore, there could be a delay in the self-administration of bronchodilator medications or a request for medical advice. This is particularly true during sleep at night, where the response to respiratory stimuli is already attenuated. Furthermore, morning dips of peak flow are particularly poorly perceived in older adults.[38] For this reason, it is prudent to advise the use of short-acting bronchodilators regularly rather than as needed. Inhaled β_2-agonists are the initial medication of choice. Antimuscarinics (e.g. ipratropium bromide) are of only limited benefit in asthma generally, but may be more successful in older adults as there is a decline in β_2-adrenoceptor density, which may make anticholinergic action relatively greater. Short-acting oral β_2-agonists are available for the small number of people unable to use any form of inhaler; however, tachycardia severely limits their use.

Inhaled glucocorticoids are the most effective maintenance therapy for asthma and many patients will

derive a good response with levels of beclomethasone (or equivalent) of 400μg daily. At this dose, the risk of systemic side effects is minimal, whereas above this dose there may be a small increase in the risk of vertebral fracture, this effect probably being less with budesonide, ciclesonide and fluticasone. Furthermore, if good control is achieved with these drugs, it may minimize the need for oral corticosteroids with their inherently greater risk profile. A spacer device will also reduce the chance of oropharyngeal candidiasis and dysphonia, while tobacco smoking limits the efficacy of inhaled glucocorticoids and must be discouraged.

Greater asthma control can be achieved with the addition of a LABA (salmeterol or formoterol) rather than stepping up the dose of an inhaled glucocorticoid. LABAs should not be used as monotherapy in asthma as they do not influence airway inflammation. For those who are still symptomatic, leukotriene modifiers are simple oral medications which have a relatively low level of side effects (reports of an association with Churg–Strauss syndrome have been largely dispelled). There is some evidence that they are effective in older adults. Controlled-release theophyllines may also be added, if asthma control is inadequate despite a high-dose inhaled steroid and LABA combination. Theophyllines have weak bronchodilator and anti-inflammatory properties, but are less potent than LABAs and have a narrow therapeutic index. It is also worth remembering that certain drugs such as beta-blockers (including topical glaucoma medication), verapamil, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) can worsen asthma symptoms.

Asthma control should be monitored by an assessment of the adequacy of symptom relief, particularly at night-time and by PEF monitoring where possible.

Inhaler technique

If good asthma control is to be achieved, it is important to consider whether the medication is being taken correctly or at all. In older people in particular, ensuring an effective inhaler technique is of the utmost importance, as without it all attempts to manage the condition are rendered useless. A full review of inhaled devices in older people is beyond the scope of this chapter, but an excellent account has recently been published by Allen.[39] Most older patients with normal cognition and no physical limitation will be able to learn to use an inhaler correctly. Difficulties in learning and coordination will be present in around 20% of cases, so it is vital to observe and correct technical faults. Further reinforcement at intervals is also important, which is partly why regular review of patients with asthma and COPD by skilled trainers is recommended in international guidelines.

One major limitation to a successful inhaler technique is poor manual dexterity, including a weak hand grip, poor coordination and impaired vision. Careful training and the use of adapters fitted to the ends of inhalers may be useful. There are many different inhaler devices available and although there is no clear winner, there may be some advantage in trying less technically complex devices.

Other key limitations are dyspraxia and cognitive impairment. More recently, impaired executive function has also been found to limit the acquisition of inhaler skills and there is an especially high incidence of this in hospitalized patients. For these individuals, the simpler the device the more chance there is of success. It is known that most patients with an abbreviated mental test score of <7 out of 10 or a Mini-Mental State Examination score of <24 out of 30 are unable to use inhalers correctly. In particular, very few, if any, patients with cognitive impairment will be able to use a metered-dose inhaler (MDI) correctly as it is a complex five-stage device.[40] In those with minor cognitive problems, it may be possible to master a four-stage inhaler correctly (MDI with a spacer) and a few patients with moderate impairment may be able to coordinate a three-stage (breath-activated) device. Being unable to copy overlapping pentagons is highly predictive of an inability to acquire an adequate inhaler technique. Carers may be able to help those with physical limitations or dementia, and nebulizers may be an alternative when all other options have been exhausted.

Key points

- COPD and asthma are common causes of symptoms and impaired health status in older adults.
- Both conditions are underdiagnosed and misdiagnosed.
- Careful history taking and spirometry can usually distinguish COPD from asthma and exclude other comorbid conditions.

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CHAPTER 51

Pulmonary hypertension

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Introduction

This chapter considers the pathology, pathophysiology and clinical aspects of pulmonary hypertension with reference to the ageing population. Elderly individuals may present with pulmonary hypertension due to any of the recognized causes, but owing to the high prevalence of cardiovascular disease, including ischaemic heart disease and chronic heart failure and respiratory disease, in particular chronic obstructive pulmonary disease (COPD), they are the main causes met with in this age group (Table 51.1).

Definition

Pulmonary hypertension is defined on the basis of haemodynamic characteristics as a mean pulmonary arterial pressure >25 mmHg at rest as assessed directly by right heart catheterization, the currently accepted 'gold standard' diagnostic method. This is a widely accepted definition that has been used in randomized controlled trials of treatment and in the pulmonary arterial hypertension registry.[1] However, recent studies in healthy individuals have shown that mean pulmonary artery pressure is 14 ± 3 mmHg with an upper limit of normal suggested to be 20 mmHg.[2] It remains unclear what the implications are for those individuals with pressures between 20 and 24 mmHg. Furthermore, the definition of pulmonary hypertension during exercise is unclear and is set rather arbitrarily at >30 mmHg.

Echocardiography is widely used in individual patients to assess the likelihood of pulmonary hypertension based on findings of impaired right ventricular function, altered haemodynamics and an estimate of pulmonary artery pressure. This is a useful assessment for suspected disease, but is too insensitive to detect mild severity pulmonary hypertension. Therefore, echocardiography is not used to define or screen for pulmonary hypertension.

Classification of pulmonary hypertension

Pulmonary artery pressure depends on multiple factors, including pulmonary vascular resistance, cardiac output and pulmonary capillary wedge pressure. Using these components, it is possible to classify pulmonary hypertension on a pathophysiological basis into pre- and post-capillary forms. Based on this classification, pulmonary hypertension was previously categorized on clinical grounds into primary and secondary types where the former did not have a clearly defined underlying cause. This classification from the 1950s has been gradually replaced by the findings of research into pulmonary hypertension, which has led to new thinking and the description of mechanisms and management strategies, particularly for primary pulmonary hypertension.

The Evian classification in 1998 grouped categories of pulmonary hypertension on the basis of shared clinical features, pathology and therapeutic options. Five groups were defined which had the effect of stimulating basic and clinical trials work in cohorts of well-defined patient types. The Third World Symposium on Pulmonary Hypertension (2003) refined the Evian scheme to incorporate an expanding understanding of the Group 1 disorder pulmonary arterial hypertension (PAH). In 2008, a further refinement was made at the Fourth World Symposium on Pulmonary Hypertension and is the classification used in this chapter.[1,3]

This increased interest in pulmonary hypertension has provided the basis for the development of expert guidelines from North America and Europe. Detailed outlines of classification and management strategies can be found in a number of these documents.[1,3,4] Thus, pulmonary hypertension is a haemodynamically defined state due to a range of pathophysiological changes that occur in the pulmonary vasculature and is associated with various clinically defined

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Table 51.1 Classification of pulmonary hypertension based on the Fourth World Symposium on Pulmonary Hypertension (2008).

Group 1. Pulmonary arterial hypertension (PAH)
Idiopathic (IPAH)
Hereditable (HPAH)
Drug and toxin induced
Associated PAH (APAH) with:
Collagen vascular disease
Congenital heart disease
HIV infection
Portal hypertension
Schistosomiasis
Chronic haemolytic anaemia
Group 1′. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis
Group 2. Pulmonary hypertension due to left-sided heart disease
Left ventricular systolic or diastolic dysfunction, valvular heart disease
Group 3. Pulmonary hypertension due to lung disease and hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Mixed obstructive and restrictive disease
Sleep disordered breathing
Alveolar hypoventilation ventilation/chronic high-altitude exposure
Group 4. Chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5. Pulmonary hypertension where causation is unknown
Haematological disorders, e.g. myeloproliferative diseases, splenectomy
Systemic disorders, e.g. lymphangioleiomyomatosis
Metabolic disorders, e.g. glycogen storage disorders, thyroid disorders
Others, e.g. chronic renal failure on dialysis, tumour emboli

conditions and is currently classified into six clinical groups (Table 51.1).

Epidemiology of pulmonary hypertension

There are few comparative data on the prevalence of different forms of pulmonary hypertension. An echocardiographic survey reported a 10.5% prevalence of pulmonary hypertension, defined as pulmonary artery systolic pressure >40 mmHg, in a group of 4579 patients. Within the group with pulmonary hypertension, ~79% had left heart disease and 10% had lung disease and hypoxia, while PAH constituted ~4% and chronic thromboembolic pulmonary hypertension (CTEPH) made up less than 1% of the group.[5]

Common features of pulmonary hypertension

Clinical presentation

The clinical presentation and investigation of pulmonary hypertension are similar for the various groups despite differences in pathology and underlying causes. The symptoms of pulmonary hypertension are non-specific and include breathlessness, a reduced exercise tolerance, weakness, fatigue, angina-like chest pain, syncope and abdominal distension. Initially, symptoms are reported on exertion, but with progression patients will report similar symptoms at rest. Later in the progress of the disorder, physical signs include a left-sided parasternal heave, an accentuated pulmonary valve component to the second heart sound and a pansystolic murmur of tricuspid regurgitation. In addition, a diastolic murmur of pulmonary regurgitation and a right ventricular third sound may be detected. Further features include jugular venous distension, hepatomegaly, peripheral oedema, cyanosis and cool extremities in the more advanced stages of the disease. Examination of the chest usually reveals perfectly normal breath sounds, but hyperinflation, hyper-resonance and a reduced breath sound intensity may indicate the presence of COPD, and fine mid to late inspiratory crackles may indicate pulmonary fibrosis or left ventricular failure. Other peripheral features may give guidance to the cause of pulmonary hypertension, for example, systemic sclerosis with telangectasia, digital ulceration.

Investigations

Electrocardiogram

The electrocardiogram (ECG) may suggest or support the presence of pulmonary hypertension demonstrating right ventricular hypertrophy and strain and right atrial dilatation. In patients with idiopathic PAH (IPAH), right ventricular hypertrophy is present in nearly 90% of subjects with right axis deviation in ~80%. Hence the absence of such findings does not exclude pulmonary hypertension and does not exclude the potential for underlying haemodynamic abnormalities. The sensitivity and specificity of the ECG makes it a poor screening tool for the detection of significant pulmonary hypertension.

Chest radiograph

The key findings are central arterial dilatation with pruning or loss of the peripheral pulmonary vessels. There may be evidence of right atrial and right ventricular enlargement, particularly in more advanced disease. The extent of radiographic abnormalities does not correlate with the level of pulmonary hypertension. In the majority of patients with IPAH, ~90% of chest radiographs will be abnormal from the time of diagnosis. The chest radiograph allows moderate to

severe lung disease and pulmonary venous hypertension due to left heart disease to be excluded or considered as the cause of pulmonary hypertension.

Pulmonary function tests and arterial gas analysis

These investigations are important as they may help to exclude underlying airways or parenchymal lung disease. Spirometry with reversibility testing or use of the post-bronchodilator FEV_1/FVC <70% criterion can be used to rule out the presence of COPD as a cause of hypoxaemia-based pulmonary hypertension. Furthermore, these investigations allow the detection of restrictive lung disease, such as interstitial lung disease. Confirmation of parenchymal lung disease, such as in predominantly emphysematous COPD and interstitial lung disease, can be determined from measurement of static lung volumes and gas transfer indices, including the transfer factor of the lungs for carbon monoxide (TLCO) and the carbon monoxide alveolar volume corrected coefficient (KCO). The physiological implication of such lung disease can be assessed from arterial gas analysis. Further evidence of parenchymal lung disease can be determined by high-resolution computed tomographic (CT) scanning. Overnight oximetry or polysomnography allows the exclusion of a number of sleep-related respiratory problems, such as obstructive sleep apnoea syndrome. Patients with PAH usually have deranged TLCO and mild to moderate reduction of lung volumes. Arterial oxygen tension in PAH is usually normal or only slightly less than normal at rest and carbon dioxide tension is decreased due to alveolar hyperventilation.

Echocardiography

This is a mandatory investigation in suspected pulmonary hypertension because a number of echocardiographic variables relate to right ventricular haemodynamics including pulmonary artery pressure, which can be estimated on the basis of the peak velocity of a tricuspid regurgitant jet. A number of extra measures can be made, such as the right ventricle to pulmonary artery systolic pressure gradient. The detection of pulmonary artery pressure is not accurate enough using this methodology to provide a suitable screening tool for mild or asymptomatic pulmonary hypertension. In the elderly, where left heart disease is likely to be the most common cause of pulmonary hypertension, echocardiographic assessment is a valuable non-invasive method. However, echocardiography can be useful in detecting the cause of suspected or confirmed pulmonary hypertension in that two-dimensional and contrast examinations may identify the presence of congenital heart disease with a shunt or dilatation of the pulmonary artery despite only moderate pulmonary hypertension. Use of transoesophageal echocardiography or cardiac magnetic resonance imaging may help to define further the nature of the problem. Left ventricular diastolic dysfunction can be assessed through the use of Doppler echocardiography.

Ventilation perfusion lung scanning

This is a recommended investigation in all patients with pulmonary hypertension to detect the presence of CTEPH, the potentially curable form of pulmonary hypertension. This is considered to be the screening method of choice for this disorder because of greater sensitivity than CT scans. A normal or low probability V/Q scan excludes CTEPH with a sensitivity of 90–100% and a specificity of 94–100%, whereas in PAH the VQ scan may be normal or show small peripheral unmatched defects in perfusion, a finding which can also occur in pulmonary veno-occlusive disease. Isotopic V/Q scanning is of little or no value in patients with airways obstruction where lung parenchymal changes lead to characteristic matched perfusion and ventilation defects.

High-resolution computed tomographic scanning

High-resolution CT scanning is useful in defining the presence of lung disease such as the emphysematous changes in COPD and the typical changes in interstitial lung disease including ground-glass shadowing, honeycombing and traction bronchiectasis. It may also be useful when investigating pulmonary veno-occlusive disease where characteristic changes of interstitial oedema with central ground-glass opacification may be seen.

Contrast computed tomographic angiography

This investigation is helpful in determining the presence of surgically accessible thromboemboli in CTEPH and can delineate typical angiographic findings such as complete obstruction or the presence of webs or bands and intimal irregularities. It is also the investigation of choice for suspected pulmonary embolism in the presence of parenchymal lung disease.

Cardiac magnetic resonance imagining

This imaging modality allows a direct assessment of right ventricular size, function and morphology. It also provides an opportunity for the non-invasive assessment of blood flow, which includes stroke volume, cardiac output, distensability of the pulmonary artery and right ventricular mass. It has the advantage of allowing repeated assessment of right heart haemodynamics and left ventricular function.

Right heart catheterization

This is necessary to confirm the diagnosis of PAH and to assess the severity of the haemodynamic impairment. Important variables that need to be assessed include the systolic, diastolic and mean pulmonary artery pressure, right atrial pressure, the pulmonary capillary wedge pressure and the right ventricular pressure. Patients with pulmonary

hypertension from other causes likely to under go transplantation should also have a right heart study. In the majority of older patients with pulmonary hypertension, the underlying cause is clear-cut and treatment is not dependent on right heart catheterization and precise knowledge of their pulmonary haemodynamic status.

Other investigations

Routine biochemistry, haematology and thyroid function tests are recommended in all patients in addition to determining their hepatitis and HIV status. Antinuclear antibodies are present in ~40% of IPAH patients, although usually at a low titre, and a number of autoantibodies should be looked for in an attempt to determine the presence of systemic sclerosis. A thrombophilia screen is important and should be performed in all patients where CTEPH is suspected. An abdominal ultrasound should be carried out to demonstrate or exclude cirrhosis or portal hypertension.

Management

There are general measures that apply to the management of most cases of pulmonary hypertension, irrespective of cause. Specific aspects of management will be discussed in the consideration of the each clinical group.

Lifestyle

General advice on activities of daily living, physical activity and diet are important in terms of general support and will help individuals adapt to and cope with the changes imposed by progressive disability. Additionally, contact with support groups may help to address the issue of increasing social isolation and the risk of anxiety or depression which commonly occur in such patients. Patients should be advised to remain active within the limitations imposed by their symptoms. In COPD, interstitial lung disease, chronic heart failure and PAH, there is evidence that supervised programmes of exercise reconditioning or full rehabilitation can improve control of breathing, exercise performance and quality of life. Combined with dietary advice, rehabilitation programmes may have an impact on the loss of peripheral skeletal muscle mass, which occurs fairly commonly in PAH, left heart disease and respiratory causes of pulmonary hypertension.[6]

Travel

There are clear guidelines regarding the assessment for and the prescription of supplementary in-flight oxygen in respiratory conditions. In general, any patient receiving oxygen therapy while living at sea level is likely to need supplementary oxygen at routine cabin pressure to maintain arterial oxygen tension and saturation. In general, a flow rate of 1–2 l min^{-1} will be sufficient.[7]

Infection

Patients with chronic lung conditions, chronic heart failure and PAH are at heightened risk of respiratory infection and pneumonia. Although there is a lack of trial evidence for all groups of pulmonary hypertension, it is generally recommended that patients receive influenza and pneumococcal immunization.

Surgery

Either elective or emergency surgical intervention in patients with pulmonary hypertension is likely to carry an increased risk of death or significant postoperative morbidity. In general, elective procedures should be undertaken with local anaesthesia whenever possible and be planned with anaesthetist colleagues.

Medical treatment

In addition to specific pharmacological treatments, especially for PAH, there are some general options that may be needed across the spectrum of pulmonary hypertension. These include the prescription of diuretics, digoxin, anticoagulants and oxygen, which may be needed intermittently or long term as background problems, such as COPD or left heart disease progress.

Pathology and pathophysiology of pulmonary hypertension

Group 1. Pulmonary arterial hypertension

The underlying mechanisms that lead to the pathological picture in this group are still largely unknown, but it is likely to be of a multifactorial origin in which there is an interaction between functional and structural components of the pulmonary vasculature. The key feature of increased pulmonary vascular resistance is likely to be due to mechanisms that lead to enhanced vasoconstriction. Much of the excessive vasoconstriction has been related to endothelial dysfunction with impaired production of vasodilator and antiproliferative factors such as nitric oxide and prostacyclin. There is also evidence of simultaneous over-expression of vasoconstrictor and proliferative substances such as thromboxane A2 and endothelin-1. This change in the balance of vasodilator and vasoconstrictor agents both leads to an elevation of vascular tone and may promote vascular remodelling by proliferative changes which enhance injury and healing mechanisms, including cellular proliferation and obstructive remodelling of the pulmonary wall, and

the presence of inflammation and the development of local thrombosis. It is probable that inflammation also has a key mechanistic role and involves complex cellular inactions between vessel wall cell populations, which is associated with a increased production of extracellular matrix proteins in the adventitia of the vessel walls. As part of the activation of the inflammatory pathways, it is likely that prothrombotic abnormalities occur that lead to the presence of thrombi in the small distal pulmonary arteries.

The characteristic pathological changes in this group are medial hypertrophy, proliferative and fibrotic changes in the intima with adventitial thickening with varying degrees of perivascular inflammatory infiltration. Complex lesions, including dilatation and plexiform formation, and thrombotic lesions may also occur. The predominant site for pathological lesions in this group of pulmonary hypertension is in the distal pulmonary arteries, generally $<500\,\mu m$ in diameter. The pulmonary veins are not usually affected in this group.

Group 1′. Pulmonary veno-occlusive disease (PVOD)

Based on histological grounds, this subgroup represents up to 10% of IPAH. The characteristic lesions are in the septal veins and the preseptal venules, which include occlusive fibrotic lesions and muscularization of the vessel walls. Varying amounts of capillary proliferation may occur with some alveolar haemorrhage and pulmonary oedema. The lymphatic system may be involved with dilatation of lymphatics and lymphadenopathy due to the vascularization of the lymph node sinus and inflammatory cell infiltration. In addition, the distal pulmonary arteries may be involved with intimal fibrosis and medial hypertrophy and occasionally complex lesions.

Group 2. Pulmonary hypertension associated with left heart disease

Amongst the mechanisms likely to increase pulmonary artery pressure is the backward transmission of the cardiac pressure elevation leading to a post-capillary passive form of pulmonary hypertension. In this variety of pulmonary hypertension, the transpulmonary pressure gradient and the pulmonary vascular resistance are within the normal range, although in some situations there is an increase in the transpulmonary pressure gradient when the pulmonary artery pressure is greater than the pulmonary capillary wedge pressure and an increase in pulmonary vascular resistance occurs from what is described as post-capillary reactive or 'out of proportion' pulmonary hypertension. The increase in pulmonary vascular resistance is likely to be due to increased vasomotor tone and possible fixed structural obstructive remodelling of the pulmonary artery resistance vessels. The increase in vasomotive tone is reversible and this is an important issue in terms of treatment while structural changes do not respond to treatment. The factors underlying these changes are not clearly understood. The characteristic changes in pulmonary vasculature in this group consist of enlarged and thickened pulmonary veins with capillary dilatation. This is associated with interstitial oedema, alveolar haemorrhage and enlargement of the lymphatics with associated enlargement of draining lymph nodes. The distal pulmonary arteries can also be affected and show features of intimal fibrosis and medial hypertrophy.

Group 3. Pulmonary hypertension secondary to lung disease and/or hypoxia

There are multiple mechanisms underlying the pathophysiological characteristics of this group, which include hypoxic vasoconstriction, the mechanical stress of hyperinflation of the lungs, the reduction of the pulmonary capillary bed coupled with chronic inflammatory changes and the likely toxic effects of cigarette smoke. There is some evidence to support an endothelium-based vasoconstrictor–vasodilator imbalance. The characteristic pathological features are in the distal pulmonary arteries where there is intimal obstructive proliferation and medial hypertrophy. Depending on the nature of the underlying lung disease, there will be a variable degree of destruction of the vascular bed, particularly in emphysematous or fibrotic areas.

Group 4. Chronic thromboembolic pulmonary hypertension (CTEPH)

The late effects of acute embolic events is the continued mechanical obstruction of the pulmonary arteries, which is likely to be the key pathophysiological process. However, there are complex background factors related to the presence of clot and systemic coagulation abnormalities leading to an enhanced risk of further thrombosis, both systemically and within the pulmonary vasculature. The characteristic lesions in this form of pulmonary hypertension are organized thrombi attached to the medial layer in the elastic pulmonary arteries, which replaces the normal intimal coat. There may be partial or complete occlusion of the lumen due to varying degrees of stenosis, web formation and band formation. In non-occluded areas, an arteriopathic change indistinguishable from that seen in PAH and plexiform lesions may be seen. In areas of complete obstruction, collateral vessels from bronchial, intercostal, diaphragmatic and coronary arteries may reperfuse the areas distal to the obstruction. The disorder can be considered as having a dual basis in the pulmonary vasculature with major pulmonary vessel obstruction and remodelling which is followed by secondary small vessel arteriopathic changes.

The latter component may offer options for treatment interventions similar to those in PAH, and some successes have been reported with such treatments.

Group 5. Pulmonary hypertension with unclear or multifactorial components

The underlying pathophysiological mechanisms of this group are likely to be multiple and generally are poorly understood. This group is extremely heterogeneous and therefore different pathological pictures are seen depending on the precise aetiological origin of the problem.

Clinical aspects of subgroups of pulmonary hypertension

Group 1. Pulmonary arterial hypertension

This is the area in the spectrum of pulmonary hypertension in which major advances in understanding of disease processes and treatment have occurred in the last 10 years. The group comprises heterogeneous disorders which share similar clinical and haemodynamic features with almost identical changes in the pulmonary microcirculation. As a consequence of the pathological processes, there is an increase in pulmonary vascular resistance which leads to right ventricular overload, hypertrophy and dilatation that progresses eventually to right ventricular failure and death. The right ventricle, which normally functions at the relatively low pulmonary arterial pressures, fails because of the limited ability of myocardial contractility to adapt to the increased resistance to outflow. This failure to respond to chronic overload leads to right heart failure with the clinical indicators of increased right atrial pressure, a reduced cardiac index and raised pulmonary arterial pressure. The increased afterload with mismatched ventricular contractility and loss of right ventricular function is a major determinant of heart failure in other forms of pulmonary hypertension.

Idiopathic PAH (IPAH) describes cases where there is no identified risk factor or family history of PAH. Hereditable PAH (HPAH) is associated with specific mutations in the bone morphogenetic protein receptor 2 (BMPR2) gene in approximately 70% of cases. However, similar germ line mutations may occur in up to 40% of patients with IPAH, indicating a potential degree of mechanistic overlap between these subgroups. Other less common mutations have been reported, such as in the transforming growth factor β gene in patients with PAH associated with hereditary telangectasia. Group 1 also includes pulmonary arterial hypertension related to drugs and toxins, such as aminorex, fenfluramine and toxic rapeseed oil, and constitutes part of the group now called associated pulmonary arterial hypertension (APAH). This group of heterogeneous disorders have a similar clinical presentation to that of IPAH and identical histological characteristics, which include the development of plexiform lesions. Based on reports from centres specializing in care of PAH, APAH accounts for approximately half the patients with PAH.

Other APAH groups are important and may be met with in older patients as a component of other underlying conditions. Collagen vascular diseases are an important subgroup in the APAH spectrum, with pulmonary hypertension being reported in rheumatoid disease, Sjogren syndrome, polymyositis, systemic lupus erythematosus, mixed connective tissue disease and systemic sclerosis. The association is most clearly established with systemic sclerosis and may have a poorer outcome than other types of PAH. Using echocardiography and right heart catheterization, pulmonary hypertension has been shown have a prevalence of up to 12% in patients with systemic sclerosis, which is probably greater than in other collagen vascular diseases. Portal hypertension, HIV infection, congenital heart disease, schistosomiasis and chronic haemolytic anaemia may be linked to APAH and require full investigation in all age groups. Full investigation is important because pulmonary hypertension may have other causes in these disorders where pulmonary fibrosis may occur, diastolic left ventricular dysfunction is common and there may be primary cardiac involvement.

Diagnosis

As in other types of pulmonary hypertension, the objective is to define the precise group into which the disorder fits. In PAH, this classification of each case is of major importance as medical management strategies are available. Hence here diagnosis is to exclude other groups and to confirm PAH, and key investigations include echocardiography, lung function tests and various imaging techniques. In the diagnosis of suspected PAH, the investigations need to cover the spectrum of likely causes and should include the possibility of referral to a specialist centre for full diagnosis and management.

Medical treatment

The majority of advances in the medical treatment of pulmonary hypertension have been made in PAH, with little progress in the more common forms of pulmonary hypertension encountered in patients with disorders such as left heart disease, pulmonary disorders or CTEPH. However, such medication is increasingly used in these disorders despite the lack of good clinical trials. Currently, the efficacy of such treatment is unclear, as are the safety issues involved. In general terms, guidelines suggest that the use of agents proven in PAH should not be used for routine treatment in other forms of pulmonary hypertension except in specialist centres.

Endothelin receptor antagonists

Endothelin-1 is a potent vasoconstrictor and mitogenic agent acting on two classes of receptors on smooth muscle and endothelial cells where its inhibition might be expected to exert some benefit in PAH. There are three main agents in this group: bosentan, an endothelin A and B receptor antagonist, sitaxentan and ambrisentan, both endothelin-A receptor antagonists. They have all been shown to have beneficial effects on aspects of pulmonary haemodynamics and wellbeing in short- to medium-term studies and there appears to be little difference in efficacy between these agents.[8] The major problem encountered with these agents has been elevation of hepatic enzymes, peripheral oedema, headache and nasal congestion and multiple drug interactions, such as warfarin, requiring the dose to be increased, ciclosporin, macrolide antibiotics and statins.

Prostacyclin analogues

Prostacyclin is a metabolite of arachidonic acid generated by the endothelium which is a potent vasodilator and inhibitor of platelet aggregation.[9] The analogue epoprostenol is given by continuous intravenous infusion and improves symptoms and exercise tolerance and in IPAH has been shown to improve survival.[10] The adverse profile of this agent includes flushing, rashes, joint pain and leg discomfort, with loose stools and headaches, and with rebound pulmonary hypertension if stopped suddenly. Iloprost is a stable inhaled and injectable prostacyclin analogue which has been shown to improve exercise capacity and pulmonary haemodynamics in PAH.[11] Adverse effects include flushing, headaches and cough. The main drawback of iloprost is its short duration of action, which may reduce its overall efficacy and necessitate frequent inhalations up to 6–9 times per day. Treprostinil and beraprost are other agents in this class showing promise in terms of treatment outcomes and improvements in stability and route of administration.

Phosphodiesterase 5 inhibitors

Sildenafil has been approved for use in patients with PAH. There have been favourable reports of benefits for patients with IPAH and APAH linked to connective tissue disorders and congenital heart disease.[12,13] Other agents in this class showing similar benefits are tadalafil and vardenafil. The main limiting factor in the use of drugs in this class are headache, flushing, dyspepsia, nasal congestion and epistaxis. An important class interaction is with nitrates, which may cause severe systemic hypotension.

Combination therapy

Combinations of the above agents have been shown to confer some extra benefits in the treatment of PAH. The potential for long-term benefits remains unknown and the issue of adverse events related to drug interactions is such that this therapy is recommended to be undertaken only in specialist pulmonary hypertension centres.[1,3,14]

Group 1′. Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis

This subgroup is without classification, although it shares some of the characteristics with IPAH. Outcomes are generally poorer then in the other subgroups of PAH and there is little evidence that treatment with drugs effective in PAH are of value. Hence lung or heart–lung transplantation is the major treatment.[15]

Group 2. Pulmonary hypertension due to left heart disease (Table 51.2)

Left heart disease is a common cause of pulmonary hypertension in the elderly and should be considered equally with respiratory causes. The main associations are with left ventricular systolic and diastolic dysfunction and valvular disease, most commonly involving the mitral valve.[16] Pulmonary hypertension has been reported in up to 60% of patients with severe systolic dysfunction and in up to 70% of those with isolated diastolic dysfunction. Pulmonary hypertension carries a poor prognosis for patients with chronic heart failure; mortality rates after 28 months of follow up are as high as 57% in patients with moderate pulmonary hypertension compared with 17% in those without pulmonary hypertension.[17]

Diagnosis

The diagnostic approach is similar to that for patients with other forms of pulmonary hypertension. Doppler

Table 51.2 Key aspects of the diagnosis and management of pulmonary hypertension associated with left heart disease.

Left heart disease may not be clinically evident, e.g. when isolated left ventricular diastolic dysfunction is present
Where appropriate right and left heart catheterization may be needed to establish the diagnosis and to exclude the possibility of PAH
Patients with an elevated pulmonary capillary wedge pressure or trans-pulmonary gradient require an assessment of vasodilator treatment on left ventricular afterload to identify an active pulmonary arterial component
Left heart disease should be treated according to established criteria and guidelines
Patients with end-stage heart disease and pulmonary hypertension may be candidates for a heart transplantation or heart lung transplantation
Drugs approved for PAH are not recommended in this group of patients as outcomes from long term clinical trials are not available

echocardiography is the key assessment when pulmonary hypertension is suspected. Left ventricular diastolic dysfunction should be ascertained in those with a dilated left atrium or atrial fibrillation and Doppler signals suggestive of changes in left ventricular haemodynamics. The following echocardiographic features of pulmonary hypertension associated with left ventricular diastolic dysfunction include evidence of left atrial enlargement, concentric remodelling of the left ventricle, left ventricular hypertrophy and evidence of elevated left ventricular filling pressures.

Treatment

There is no specific treatment for pulmonary hypertension related to left heart disease. However, a variety of therapeutic options including diuretics, nitrates, hydralazine, ACE inhibitors and other interventions including left ventricular assist devices, corrective valvular surgery, resynchronization therapy and heart transplantation have been used to lower pulmonary artery pressure through reducing the left ventricular filling pressure. Hence, for the majority of patients the management of pulmonary hypertension secondary to left heart disease should be the optimal treatment of the underlying cardiac disease in accordance with accepted guidelines. Patients with end-stage heart disease and chronic heart failure with accompanying pulmonary hypertension may be candidates for a heart transplantation or heart–lung transplantation.

A few studies have examined the efficacy of drugs currently recommended in PAH. Randomized controlled trials with epoprostenol and bosentan for advanced heart failure had to be terminated early due to the increased rate of adverse events in the treated group compared with conventional therapy. It has been suggested from small studies that sildenafil may improve exercise capacity and quality of life. Current international guidelines do not recommend the use of PAH-specific drugs in this form of pulmonary hypertension until more robust and longer term studies have been completed.[1]

Group 3. Pulmonary hypertension due to lung disease and/or hypoxia (Table 51.3)

Pulmonary hypertension is a common late component of respiratory diseases where hypoxia is a prominent feature, such as COPD, interstitial lung disease and obstructive sleep apnoea. The presence of pulmonary hypertension in patients with COPD leads to a reduced survival and more frequent symptomatic exacerbations. It is also a poor prognostic factor in patients with interstitial lung disease and pulmonary artery pressure is an important predictor of mortality.

The prevalence of pulmonary hypertension in COPD depends on the definition of COPD and its severity and also the definition of pulmonary hypertension. The majority of studies of pulmonary haemodynamics in this area are generally in patients with advanced lung disease, indicated by severe or very severe airways obstruction with a forced expiratory volume in 1 s (FEV_1) less than 40% predicted.[18] In a group of 120 patients with a mean FEV_1 of 27% predicted, pulmonary hypertension, defined as a mean pulmonary artery pressure >20 mmHg, occurred in 91% of the patients. However, the majority of these patients had only mild to moderate severity pulmonary hypertension with pulmonary artery pressures of 20–35 mmHg.[19] An interesting finding was the overlap of probable left heart disease with airways obstruction In this group, the mean pulmonary artery pressure was more closely related to pulmonary capillary wedge pressure than it was to FEV_1 or arterial oxygen tension, which suggests that there was significant left ventricular diastolic dysfunction in this severe COPD subgroup. This may be explained by increased aortic stiffness, which occurs in COPD and is a predictor of diastolic dysfunction in such patients.[20,21] In a larger study of nearly 1000 patients with COPD, severe pulmonary hypertension with a mean pulmonary artery pressure of >40 mmHg occurred in only 27 patients out of 998 and the majority of these patients had alternative causes for their pulmonary hypertension. This group of patients with COPD had much less severe airways obstruction than in the smaller study with an FEV_1 of ~50% predicted, although they had evidence of hyperventilation,

Table 51.3 Key aspects of the diagnosis and management of pulmonary hypertension in chronic lung disease.

Suspect pulmonary hypertension when:
Symptoms are more severe than expected from impairment of lung function
Right heart dysfunction is present
Profound hypoxaemia, hyperventilation or a low transfer factor is present
Doppler echocardiography is the best non-invasive assessment
Right heart catheterization only if pulmonary hypertension is likely to affect the management of the chronic lung disease
Appropriate patients with severe pulmonary hypertension, >35 mmHg with or without right heart failure may benefit from review at a specialist pulmonary hypertension centre
Treat lung disease optimally according to National Guidelines, including long-term oxygen therapy for severe chronic hypoxaemia
There is no evidence of benefit or safety in pulmonary hypertension secondary to chronic lung disease for drugs used in the treatment of PAH. Use of such drugs should be initiated and monitored at a specialist pulmonary hypertension centre

hypoxaemia and a reduced diffusion capacity. Importantly, the survival time of these patients was less than that in the other patients with COPD and pulmonary artery pressures between 20 and 40 or <20 mmHg.[22] This finding suggests that there is a subset of patients with 'out-of-proportion' pulmonary hypertension. These two studies have been complemented by further studies which again have shown high levels of pulmonary hypertension in patients with severe airways obstruction, but the in the majority of patients only mild to moderate elevation of pulmonary artery pressure. Again, a subset of patients with 'out-of-proportion' pulmonary hypertension was identified.[23] The importance of identifying this subgroup is their poorer survival and, because they appear to share some features with IPAH, they may be potentially treatable with medication proven to be effective in PAH. The true prevalence of pulmonary hypertension in COPD remains unknown, but it has been suggested that if a cut-off mean pulmonary artery pressure of >20 mmHg is taken as the basis for defining pulmonary hypertension, then the prevalence is in the region of 100–150 per million patients.

Important features of pulmonary hypertension in COPD that distinguish it from PAH are that in general the degree of pulmonary hypertension is in the mild to moderate range, generally <35 mmHg, that the progression of pulmonary hypertension is slow in these patients and that they develop right ventricular diastolic dysfunction with the features of cor pulmonale dominating. Cardiovascular complications also separate PAH from COPD-related pulmonary hypertension. Low cardiac output due to right ventricular forward failure is common in late-stage PAH, but is uncommon in COPD, where the link to death due to a cardiovascular mechanism is often the outcome of ischaemic heart disease.

Diagnosis

Similarly to the diagnosis of other forms of pulmonary hypertension, Doppler echocardiography is the best option for non-invasive diagnosis. Systolic pulmonary artery pressure can be estimated from the maximum velocity of the tricuspid regurgitant jet. A key limitation of this approach is that many patients have a degree of hyperinflation and the estimated pressure is not reliable for diagnosis of mild pulmonary hypertension. In the setting of dilated left atrium, atrial fibrillation or characteristic changes in mitral flow profile or pulmonary venous flow profile and left ventricular hypertrophy, then diastolic dysfunction should be suspected and sought.

'Out-of-proportion' pulmonary hypertension should be considered in patients with COPD of milder severity airways obstruction who demonstrate severe hypoxaemia, hypocapnia and a decreased TLCO with severe pulmonary hypertension and no other apparent cause.

Treatment

Currently, there is no specific therapy for pulmonary hypertension associated with chronic lung diseases including COPD and interstitial lung disease. Treatment of airways obstruction should be optimized with both lifestyle modification, such as smoking cessation and exercise prescription, and appropriate pharmacotherapy according to national and international guidelines.[18]

As alveolar hypoxia is a major factor in the development of pulmonary hypertension, this should be addressed with long-term oxygen therapy (LTOT). Two studies, the Nocturnal Oxygen Therapy Trial (NOTT) in the USA and the Medical Research Council (MRC) trial in the UK both demonstrated improved survival for patients with late-stage severe COPD. Both studies included an initial assessment of pulmonary haemodynamics and a follow-up assessment in a subgroup of patients after a period of time on treatment. In the MRC group, over 1 year LTOT was associated with no increase in mean pulmonary artery pressure compared with controls receiving air, where mean pulmonary artery pressure increased by 2.8 mmHg per year. In the NOTT study, LTOT for >18 h per day was associated with a reduction in mean pulmonary artery pressure both at rest and during exercise, whereas LTOT for 10–12 h per day had no effect. In addition, LTOT will partially reduce the progression of pulmonary hypertension in COPD, but pulmonary artery pressure rarely returns to normal values with this treatment and the structural abnormalities of the pulmonary vasculature remain largely unchanged. There is no evidence that earlier use of LTOT in patients with COPD and isolated episodes of hypoxaemia, such as during sleep, has any effect on the development of pulmonary hypertension and oxygen should be prescribed within defined guidelines. Thus LTOT for >16 h per day, the UK recommendation, will generally stabilize pulmonary hypertension and may slow its progression in COPD. The role of LTOT in interstitial lung disease and other respiratory disorders is much less clear, as trials have not been carried out to demonstrate benefit.

Drugs with demonstrated specific benefits in PAH have not being fully assessed in patients with pulmonary hypertension secondary to respiratory disease; there are few studies to support their use and those published have been uncontrolled. Use of vasodilator agents is not recommended owing the potential impairment of gas exchange if hypoxic pulmonary vasoconstriction is reduced. Further properly constructed randomized controlled trials of treatment are required before drugs for PAH can be recommended for use in pulmonary hypertension secondary to respiratory disease.

Patients with 'out-of-proportion' pulmonary hypertension associated with lung disease should be referred to specialist centres for further investigation and the possibility of treatment with PAH-specific drug therapy.

Group 4. Pulmonary hypertension secondary to venous thromboembolism (Table 51.4)

Chronic thromboembolic pulmonary hypertension (CTEPH) results from a single or recurrent thromboemboli arising from sites of venous thrombosis, which lead to non-resolving pulmonary vascular obstruction. It is associated with considerable morbidity and mortality and is estimated to occur in 0.15–0.5% of patients surviving an acute pulmonary embolism, but a prospective study cohort revealed that 3.8% of survivors developed CTEPH within 2 years of the acute embolic event. However, such estimates are of limited value as the many patients with CTEPH do not experience an acute pulmonary embolus. The cumulative incidence after an acute pulmonary embolus has been suggested to be in the region of 1–4% between 2 and 4 years after the initial embolic event. Because of the hidden nature of the problem in most patients, it is essential to consider this as a diagnosis as soon as any evidence of pulmonary hypertension occurs. Accepted risk factors for CTEPH include splenectomy, central lines, inflammatory bowel disease and ventriculoatrial shunts.

There is evidence that pulmonary emboli either in their overt acute form or in an occult form trigger a cascade of events that lead to CTEPH. In the majority of patients following a pulmonary embolus, there is a return to normal haemodynamics within 4–6 weeks.[24] However, based on lung perfusion and echocardiographic analysis, up to 25% of patients will have evidence of persistent pulmonary hypertension or abnormal lung perfusion patterns.[24] Hence it is likely that there is incomplete recovery from acute pulmonary embolus and that this is often unrecognized and leads to the risk of developing CTEPH.

Table 51.4 Key aspects of the diagnosis and management of pulmonary hypertension secondary to chronic thromboembolism.

Ventilation perfusion scans necessary for unexplained pulmonary hypertension as normal or near-normal perfusion largely excludes CTEPH
Patients with a history or findings suggesting CTEPH and are candidates for pulmonary endarterectomy should be referred to centres with expertise in investigation and surgery in this condition
Pulmonary endarterectomy is the preferred and only curative treatment for CTEPH
In severely compromised patients, surgery may not be an immediate option. Medical therapy with a range of treatments to improve haemodynamics and clinical performance should be undertaken, ideally at a specialist centre
Patients with inoperable disease, such as with peripheral thromboembolism, may be candidates for medical therapy and should be reviewed at a specialist centre
Some patients with CTEPH may benefit from drugs currently used in PAH, but there are no definitive studies and such care should be delivered in specialist centres

Diagnosis

In the setting of a known previous pulmonary embolus, persistent or recurrent breathlessness should be regarded as indicating the potential for CTEPH. The key investigation is currently two-dimensional echocardiography with Doppler flow studies to evaluate the likelihood of raised pulmonary artery pressure, defined as a pressure >25 mmHg at rest or >30 mmHg with exercise. If a raised pulmonary artery pressure is present, further evaluation should include oxygenation, full pulmonary function testing, a high-resolution CT scan of the chest, ventilation perfusion scanning of the lungs and cardiac catheterization.[1,4] The definitive investigation for CTEPH is right heart catheterization, which gives the direct measurement of pulmonary pressures. The measurement of circulating amino-terminal pro-brain natriuretic peptide and troponin have been used to exclude both preclinical and symptomatic CTEPH in patients known to have previously had a pulmonary embolus. The use of a VQ scan is essential because it has a higher sensitivity than a CT pulmonary angiogram in detecting the presence of CTEPH.

Treatment

Diagnosis of CTEPH is an indication for life-long anticoagulant prophylaxis with warfarin. It is generally recommended that the international normalized ratio (INR) is kept between 2 and 3 to prevent further thromboembolic episodes.

Surgical treatment

This is the treatment of choice, because CTEPH is potentially curable with pulmonary endarterectomy.[25] Selection of patients for surgical treatment is important, with reported mortality rates for patients undergoing this treatment ranging from 5 to 24%. An important factor in this wide range is that most patients present in a late phase of their disease and may not be suitable for endarterectomy or are of borderline suitability. The presence of predominantly distal embolization and in patients with severe comorbidities, who are not candidates for surgical correction, medical treatment options need to be explored. The outcomes of surgery are generally good with regard to quality of life, overall functional status, haemodynamics and right heart function. However, an important determinant of the outcome of surgery is the extent of small vessel arteriopathy.[26,27] Up to 15% of patients operated on will have continuing pulmonary hypertension and should be considered suitable for additional medical therapy.

Medical treatment

Three major pathways of treatment have been used in patients with advanced CTEPH or peripheral emboli not suitable for surgical intervention. These agents can be used as monotherapy or in combinations. The individual treatments are endothelium receptor antagonists (ERAS), prostacyclin analogues and phosphodiesterase inhibitors to inhibit breakdown of nitric oxide. Most reports of such treatment in CTEPH are open label and currently only one randomized controlled trial has been reported with improvements in pulmonary vascular resistance at 4 months, but with no improvement in the 6 min walking distance, which suggest little improvement in functional capacity. Additionally, there was no difference to placebo in terms of time to clinical deterioration in a group of inoperable CTEPH patients. At present, there is insufficient evidence for the introduction of such drugs into the general care of CTEPH and their use is recommended to stay within specialist centres and in clinical trials of treatment.[1,4]

Group 5. Pulmonary hypertension where cause is unknown

The clinical presentation of pulmonary hypertension is similar to that in other groups, as are the diagnosis and investigations. The association of pulmonary hypertension with other disorders complicates the issue of treatment, which should be of the associated disorder. Little is known of the use of PAH recommended drugs in this group and referral to a specialist centre may be appropriate.

Conclusion

Pulmonary hypertension is not uncommon in the elderly and is usually associated with cardiovascular and respiratory disorders, although other causes should be considered. In the majority of patients, the treatment is of the underlying disorder, but in more complex cases referral to specialist centres is an important option.

Key points

- Pulmonary hypertension occurs in the setting of left heart disease with either ventricular dysfunction or valvular decompensation and chronic destructive respiratory diseases, such as chronic obstructive pulmonary disease and chronic thromboembolic disease.
- Recent increased knowledge of pathophysiological mechanisms underlying pulmonary hypertension and the development of new investigative tools have led to a clinicopathological classification of pulmonary hypertension.
- Pulmonary arterial hypertension is a group of hereditable, idiopathic and other specific forms of pulmonary hypertension that lead to small arteriolar disease. There have been significant developments in the treatment of this group, which as yet have not become part of the accepted standard treatment of the other groups of pulmonary hypertension.
- The elderly may develop pulmonary hypertension from any of the recognized causes, but still the major associations will be with cardiorespiratory disease.

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CHAPTER 52

Pulmonary rehabilitation

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Introduction

Pulmonary rehabilitation is 'an evidence-based, multidisciplinary and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities'.[1] Pulmonary rehabilitation has been used for decades, but its acceptance has only recently become widespread. In part, this is due to the experience with lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD). In the National Emphysema Treatment Trial (NETT), pulmonary rehabilitation was a component of standard therapy for patients undergoing surgery. In a review of the experience of NETT patients in pulmonary rehabilitation, in addition to demonstrating the efficacy of LVRS in a subset of patients with severe emphysema, it showed that widespread use of pulmonary rehabilitation resulted in substantial benefit for patients with COPD.[2] This was the first study to demonstrate the efficacy of pulmonary rehabilitation across a large number of sites. Based on this, pulmonary rehabilitation has become standard of care both before and after LVRS. In addition, patients must participate in pulmonary rehabilitation both before and after lung transplantation.

Pulmonary rehabilitation has been slow to gain acceptance. It has never been shown to improve survival in patients with COPD. In addition, no consistent improvement in lung function has been demonstrated and oxygenation does not improve with pulmonary rehabilitation. Unfortunately, in the past, many practitioners interpreted these results as indicating that pulmonary rehabilitation was not beneficial. This was a result of a misconception about the goals of pulmonary rehabilitation. Patients with chronic lung disease suffer from chronic dyspnea, which leads to a reduction in daily activities and increased social isolation. This can contribute to the development of mood disturbances, which are very common in patients with COPD. When these outcomes are studied, the benefits of pulmonary rehabilitation become clear. Multiple studies of pulmonary rehabilitation have demonstrated significant improvements in exercise tolerance, endurance, symptoms of dyspnea, psychosocial well-being and quality of life, all of which are meaningful endpoints for patients suffering from this chronic disease. Awareness of pulmonary rehabilitation varies by region and even from practitioner to practitioner in a given area. In the USA, the Centers for Medicare and Medicaid Services recently granted a procedure code and national coverage determination for pulmonary rehabilitation. This has also raised awareness of pulmonary rehabilitation, partly as a business opportunity, but has also validated the hard work of many professionals who have advocated the benefits of this treatment modality.

Organization

There are no specific guidelines for the organization or structure of a pulmonary rehabilitation programme. A multidisciplinary approach is required with involvement from nursing, physical therapy, occupational therapy and respiratory therapy. Psychologists or social workers may also be employed, in addition to nutritionists and recreational therapists. A physician serves as the medical director. The medical director's role includes performing the initial screening, writing the exercise prescription and monitoring the patients' progress through the programme. The director is also available for emergency situations. The director acts as an educator to the staff and patients and may also be a research coordinator. One member of the team serves as the programme director and is responsible for the day-to-day management of the programme, recruitment and marketing.

The location of the programme varies. Although it is most often based in the outpatient setting as either a hospital-based or free-standing facility, it can also be performed in an inpatient setting or even at the patient's home. A typical programme lasts for 8–12 weeks with 2 h sessions performed two to three times per week. Components of

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a pulmonary rehabilitation programme include exercise, education and psychosocial support.

Patient selection

In general, patients with symptomatic chronic lung disease are likely to benefit from pulmonary rehabilitation. It was initially developed for patients with COPD over 30 years ago and much of the literature on the effects of pulmonary rehabilitation is based on its effect in this patient population. Recently, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classified COPD into four stages, depending on the magnitude of reduction in the forced expiratory volume in 1 s (FEV_1).[3] Patients with GOLD class II–IV [FEV_1 <80% of predicted with a forced vital capacity (FVC) to FEV_1 ratio of less than 70%] are eligible to participate in pulmonary rehabilitation.

The prevalence of COPD increases steadily with age. It is difficult to get an accurate estimate of COPD prevalence in the elderly because the FEV_1/FVC ratio declines with age. As a result, some elderly normal patients may be classified as having COPD by the GOLD criteria. The National Center for Health Statistics in the USA estimated the incidence of COPD in elderly adults at just less than 10%.[4] Rates in other countries may vary and many other factors may contribute to prevalence rates. For example, in China, prevalence rates increase significantly with age with 2.3% of those aged 40–49 years meeting the spirometric definition of COPD, whereas in those over 70 years of age the prevalence was 20.4%.[5] Urban versus rural location, body mass index, level of education and amount of ventilation in a person's kitchen also affected prevalence rates.

Not surprisingly, elderly patients with COPD comprise the majority of patients participating in most pulmonary rehabilitation programmes. In recent years, there has been increased interest in extending pulmonary rehabilitation to patients with other respiratory conditions. These patients also suffer from deconditioning, dyspnea, impaired health status and quality of life. Pulmonary rehabilitation has been used in patients with restrictive and interstitial lung diseases, bronchiectasis, asthma, chest wall disorders and pulmonary hypertension.[6–9]

Historically, pulmonary hypertension has been considered a contraindication to pulmonary hypertension. With exercise, especially static, resistive exercise, there is a significant increase in right and left ventricular overload. In patients with pulmonary hypertension, due to fixed pulmonary vascular constriction, this may lead to a dramatic rise in pulmonary arterial pressure without a rise in cardiac output, which may lead to circulatory failure. Recent experience has not supported this notion. Many patients with pulmonary hypertension related to other chronic pulmonary conditions (World Health Organization group III) exercise in pulmonary rehabilitation without complication. Furthermore, with the advent of numerous advanced therapies for pulmonary arterial hypertension (World Health Organization group I), it seems that these patients may exercise safely at submaximal exercise levels.

Owing to the increased utilization and literature now supporting the use of pulmonary rehabilitation for other chronic respiratory conditions, the latest version of the American College of Chest Physicians and American Association of Cardiovascular and Pulmonary Rehabilitation (ACCP/AACVPR) practice guidelines for pulmonary rehabilitation state that 'pulmonary rehabilitation is appropriate for any stable patient with a chronic lung disease who is disabled by respiratory symptoms'.[10]

Components of pulmonary rehabilitation

Exercise

Exercise training is the cornerstone of pulmonary rehabilitation. Patients with chronic dyspnea frequently have low activity levels. With progressive dyspnea, disuse atrophy develops resulting in significant skeletal muscle deconditioning. This, in turn, leads to further curtailment of activities with worsening of symptoms. Numerous studies have demonstrated improvements in dyspnea and exercise capacity in patients with COPD. These studies do not demonstrate a corresponding increase in lung function, indicating that these gains are related to a conditioning effect.

Exercise can focus on either endurance training or strength training. Both are beneficial for patients with chronic lung disease. Activities such as walking or biking require endurance training and patients will show significant improvements in 6 min walk distances after pulmonary rehabilitation. Many patients with chronic lung disease complain of shortness of breath on getting out of a chair, lifting objects or reaching over their heads. As a result, strength training has been added to pulmonary rehabilitation programmes; however, the scientific basis for doing so is limited, with studies demonstrating that strength training increases muscle mass but with no clear clinical benefit.

Anabolic steroids have been investigated in patients with COPD. These patients often have reduced muscle mass compared with age-matched, healthy controls. In several studies of testosterone, nandrolone and stanozolol, there have been variable improvements in lean muscle mass but no improvement in endurance or symptoms of shortness of breath. As a result, these are not recommended as adjunctive treatment in pulmonary rehabilitation.

Pre-enrolment cardiopulmonary exercise testing is performed to help design an exercise programme for patients. Exercise sessions usually last from 20 to 40 min at a

time. Exercise can be of either high or low intensity. High-intensity exercise produces greater improvements in exercise capacity than low-intensity exercise during pulmonary rehabilitation but, in general, is not as well tolerated. This is especially true in elderly patients who may have coexisting neurological disorders or gait instability affecting the ability to perform high-intensity exercise. Other issues related to age that may influence the ability to perform exercise include limited shoulder mobility, tremor and medication effect. Despite this, pulmonary rehabilitation has been shown to be as effective in older patients as it is in younger patients.[11] Older patients (aged >70 years) showed similar improvements in walk distances, dyspnea and quality of life scores to those of younger patients.

Education

Education is an integral component of pulmonary rehabilitation. Patients benefit from an understanding of their disease and learn how to recognize symptoms of an exacerbation. Better coping skills, better understanding of the physiological and psychological aspects of chronic pulmonary disease, better adherence and understanding of medications and other treatments and smoking cessation are also potential benefits of the educational component of pulmonary rehabilitation. Education, however, is no substitute for exercise in pulmonary rehabilitation. A number of randomized studies have compared education and exercise in patients with COPD. In these studies, dyspnea and exercise tolerance were greater in the exercise treatment arm whereas little benefit was seen in those receiving education alone.

Specific topics of the education component of pulmonary rehabilitation can include a review of available medications, teaching of inhaler technique, lung function, basic pathophysiology of pulmonary diseases, oxygen therapy including travel, nutrition and stress management. In addition, pulmonary rehabilitation can provide a unique opportunity to discuss advanced directives including educating patients on healthcare proxies, living wills, palliative care and physician–patient communication regarding end-of-life issues.

Psychosocial support

Anxiety, depression and difficulty in coping with the progressive, debilitating nature of chronic lung disease are common in these patients. In part, this is due to loss of independence as symptoms worsen. This can lead to progressive social isolation and a sense of hopelessness. The elderly are particularly at risk since their spouses may also be disabled or no longer surviving. In addition, their children may be grown up and not available to help with their daily activities. Chronic dyspnea can lead to both anxiety and panic. This can cause patients to avoid leaving their homes due to fear of being away from a comfortable environment in which they can pace themselves and have ready access to medication if needed. This can worsen social isolation and contribute to depression.

Depression is commonly identified in patients participating in a pulmonary rehabilitation programme. There is limited literature on the effect of pulmonary rehabilitation on psychological outcomes. In a few trials, following pulmonary rehabilitation, patients had fewer symptoms of anxiety and depression and showed improved cognitive function.[12] The latest ACCP/AACVPR guidelines on pulmonary rehabilitation recently raised the evidence grade for psychosocial support in pulmonary rehabilitation to grade 2B (weak recommendation with moderate supporting evidence).

Psychological support during pulmonary rehabilitation can be in the form of regularly scheduled support groups focusing on specific topics such as stress reduction, coping skills or control of panic. Family sessions are often also included in these programmes. Group sessions, progressive relaxation techniques and hypnosis have all been tried in these, with anecdotal reports of success.

Outcomes

Studies of pulmonary rehabilitation have consistently shown improvements in exercise tolerance as measured in walking distance, quality of life and dyspnea. As mentioned above, these programmes also seem to help patients control anxiety and reduce symptoms of depression. Measures of peak exercise capacity, such as maximal oxygen consumption, with exercise are not clearly improved with pulmonary rehabilitation, but sustainable exercise, reflected by the 6 min walk distance, correlates with improved quality of life. Most of these improvements can be accounted for by changes in muscle strength and oxidative capacity. Improvements in dyspnea and exercise tolerance can also be due to both a reduction in fear and desensitization to dyspnea which occur independently of training effect.[13] Despite these effects on exercise capacity and quality of life, there is no effect on survival in patients with chronic lung disease. Pulmonary rehabilitation also has no effect on pulmonary function or oxygen requirements. Because of this, pulmonary rehabilitation should be considered as one of many potential treatments available to the physician but it is not a replacement for effective pharmacological therapy.

Another significant effect of pulmonary rehabilitation, and one that helped third-party payers agree to reimburse for pulmonary rehabilitation, is the effect that it has on reducing healthcare utilization. In a single centre in Wales, patients completing pulmonary rehabilitation had fewer hospital days (10.4 versus 21) for the year following

rehabilitation compared with patients not participating in pulmonary rehabilitation.[14] In the USA, similar results were seen in California. At 10 sites throughout the state, there was a significant reduction in hospital days the year after rehabilitation compared with the year before (3.4 versus 10). There were also fewer physician visits, telephone calls and urgent care visits the year following pulmonary rehabilitation.[15]

Maintenance following pulmonary rehabilitation

The benefits of pulmonary rehabilitation, although significant, are generally lost over time. Both in our experience and in multiple trials of pulmonary rehabilitation, the gains made generally fade over ~12–18 months following completion.[16] The benefits in dyspnea and quality of life usually last longer than those in improved exercise capacity. This may be related to the educational components of pulmonary rehabilitation and the sense of mastery that patients acquire during the programme. This is more enduring than the physiological effect of exercise training that occurs during pulmonary rehabilitation. It is common for patients, after a short-term, high-intensity programme, to return to a sedentary lifestyle. Some highly motivated patients will follow a post-rehabilitation exercise programme and have sustained benefits, but this is not the norm.

Some pulmonary rehabilitation centres have developed maintenance programmes to allow patients to exercise in a structured programme. This also maintains the social element of the rehabilitation environment, which acts as a motivating factor. These programmes are not as well standardized or rigorous as formal pulmonary rehabilitation programmes. Education and psychological support are usually not included in maintenance programmes.

There are many challenges to developing maintenance programmes, the foremost of which is lack of reimbursement. There is little literature supporting the use of maintenance programmes. Difficulties in assessing the efficacy of maintenance programmes include the effects of intercurrent illness which is likely to occur over a prolonged course of maintenance, loss of interest, difficulties in transportation and cost of the programme to patients. Any outcomes of maintenance will be biased by the fact that only the most motivated patients will participate over a prolonged period.

Pulmonary rehabilitation ultimately is an attempt to generate a lifestyle change for patients by using education and exercise that are specifically designed to maximally benefit those with chronic respiratory disease. Unfortunately, it is difficult to achieve lifestyle changes during a short, 6–12 week programme. Inpatients who underwent repeated pulmonary rehabilitation programmes on a yearly basis had similar benefits compared with the initial cycle; however, these benefits dissipated over the following year. Long-term lifestyle modification requires a short-term, high-intensity intervention followed by continued reinforcement. Therefore, although rehabilitation has significant effects on quality of life and exercise capacity, without some form of maintenance patients are likely to gradually return to their previous level of disability.

Conclusion

Pulmonary rehabilitation produces improvements in exercise capacity and respiratory symptoms in patients with chronic respiratory disease, even in those receiving optimal medical therapy. Spurred in part by the experience with lung volume reduction surgery, pulmonary rehabilitation has become recognized as standard of care for patients with COPD. Unlike lung volume reduction or transplantation, which is indicated for only a small percentage of patients with COPD, pulmonary rehabilitation can be used in a wide range of patients with COPD. Furthermore, because of the significant benefits in patients with COPD, it is also being increasingly utilized for patients with other respiratory conditions, with similar success.

Key points

- Dyspnea is multifactorial and not necessarily related to impaired lung function alone. Deconditioning, changes in skeletal muscle function with COPD, electrolyte imbalance and the cardiovascular effects of hyperinflation also contribute to exercise intolerance.
- Pulmonary rehabilitation is a multidisciplinary programme which specifically addresses many of these issues in patients with chronic respiratory disease.
- Pulmonary rehabilitation improves exercise capacity, dyspnea and quality of life in patients with chronic respiratory disease. It also helps to reduce healthcare utilization.
- The effects of pulmonary rehabilitation gradually fade without continued reinforcement. Maintenance programmes may help sustain the gains made during pulmonary rehabilitation.
- Although initially developed for patients with COPD, pulmonary rehabilitation should be considered for all patients with symptomatic chronic respiratory disease.

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SECTION 6

CNS Disorders

CHAPTER 53

Neurological signs of ageing

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Introduction

Any attempt to describe the neurological signs of ageing immediately prompts a number of challenging questions. Perhaps the most pertinent of these is how to ascribe neurological signs observed in later life to normal ageing *per se*, rather than concurrent (and possibly subclinical) age-related neurological conditions such as cerebrovascular disease, Alzheimer's disease (AD), Parkinson's disease or combinations thereof. Differing quantitatively or qualitatively from normal ageing, such diseases fall within the purview of geriatric neurology. From the clinical perspective, this is not merely a question of dry academic interest, since disease-related changes might be amenable to disease-specific therapeutic interventions, whereas age-related change might require acceptance as part of the human condition, perhaps abetted by sympathetic attempts at neurorehabilitation.

To define the neurological signs of normal ageing, one requires a definition of 'normal', which will determine the optimal requirements for a study which aims to describe such signs. The one absolute of studies of ageing is substantial heterogeneity, in both control and age-related disease groups. Hence it must be decided if individuals selected for study should be free of all age-related disease and medication use. Such individuals may be described as having undergone 'successful' ageing or 'optimal' ageing. By contrast, the category of 'typical' ageing accepts common age-associated disease (and medication use) as physiologically typical of the ageing process. Such definitions may be informed by biological models of ageing, such as senescence (age as a disease) or lifespan (age as development) models. Considerations of this nature will also determine the locus of study populations (community based, hospital based, nursing home based) and whether an attempt should be made to include all relevant subjects or only those who volunteer for study.

'Successful' ageing or 'optimal' ageing occurs in 'supernormals,' individuals whose function or performance clusters at the upper end of any normal distribution. Genetically, these individuals may differ from those undergoing 'typical' or 'normal' ageing. Relatively greater or lesser vulnerability of ageing tissues to disease processes and relative preservation or loss of neural regenerative capacities with ageing[1] may also be relevant.

Study logistics also need careful consideration. Cross-sectional studies, in which, for example, 20-year-olds are compared with 50- and 80 year-olds, with assessment occurring at one time point, may overestimate age-related changes because of cohort effects such as differences in education or nutrition. Moreover, with lack of follow-up, it may be that 'normals' in the older age groups were in fact in the subclinical phase of age-related disease. Longitudinal studies of cohorts which might address such difficulties, by following individuals for many years with repeated examinations at successive time points, risk underestimating change due to loss of subjects to follow-up. Such studies are also expensive, sometimes prohibitively so.

The definition of signs to be examined and standardization of testing procedures are also fundamental requirements. Disagreement between experienced examiners in the interpretation of neurological signs is well recognized.[2,3] Hence prespecified operationalization of neurological examination and agreement on scoring or quantitation of signs are required for robust results.[4] Without specifying these parameters, it is difficult to realize a quantitative measure of the sensitivity and specificity of neurological signs with respect to ageing.

Similar arguments apply to age-related changes in investigation findings, such as neuroimaging and electrodiagnostic studies, and likewise to the definition of the neuroanatomical substrates of change in neurological signs with ageing. For example, cerebral atrophy on structural brain imaging or in postmortem tissue is not an uncommon

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finding in cognitively normal older individuals and is not in itself an inevitable signature of AD.[5,6]

Neurological signs of ageing

An early and comprehensive review of the neurology of old age was given by Critchley in his three Goulstonian Lectures delivered to the Royal College of Physicians of London in March 1931.[7] Since then, many reviews have appeared, some indicating the need to revise the designation of 'senile' for certain signs in favour of aetiological explanations which may carry therapeutic implications.

Some neurological signs particularly associated with ageing are briefly described (summarized in Table 53.1), along with details of their investigational correlates and neuroanatomical substrates where these are known. Techniques for eliciting neurological signs and their semiological value are not covered here.[8] The description follows the traditional, and somewhat arbitrary, sequence of the neurological examination.

Table 53.1 Topographical overview of age-related neurological signs.

Cognitive function:
- Loss of processing speed, cognitive flexibility, efficiency of working memory (sustained attention)
- Preservation of vocabulary, remotely learned information including semantic networks and well-encoded new information

Cranial nerves:
- I: olfactory sense diminished
- II: presbyopia; reductions in visual acuity, depth and motion perception, contrast sensitivity
- III, IV, VI; senile miosis; restricted upward conjugate gaze
- VIII: presbycusis; impaired vestibulospinal reflexes

Motor system:
- Appearance: loss of muscle bulk; 'senile tremor'
- Tone: rigidity, *gegenhalten*/paratonia; mild parkinsonism
- Power: decline in maximum muscle strength
- Coordination: impaired speed of movement
- Reflexes: depressed or absent phasic muscle stretch reflexes (especially ankle jerk); depressed cutaneous reflexes (e.g. abdominal); emergence of primitive or developmental reflexes (glabellar, snout, palmomental, grasp)

Sensory system:
- Decreased sensitivity to vibratory perception, +/− pain, temperature, proprioception

Cognitive function

Ageing has both structural and functional effects on the brain.[9] Serial registered magnetic resonance imaging scans show that there is a decrease in global and regional (temporal lobe, hippocampus) brain volumes, the rate of which may increase after the age of 70 years.[5] Hence brain atrophy *per se* is not specific for the diagnosis of pathological change, an assumption which may lead to clinical misdiagnosis of AD if undue weight is placed on structural neuroimaging findings.[6] The neuroanatomical correlates of this volume loss are uncertain, possibly including neuronal loss or shrinkage, dendritic pruning and synaptic loss and white matter change. There is also evidence for plasticity in the ageing brain, with dendritic sprouting which may help to maintain synaptic numbers, although such compensatory abilities may decline with age. Vascular change becomes more frequent in the ageing brain, as manifested by leukoaraiosis (small vessel ischaemic change in white matter) and silent infarcts, possibly related to rises in blood pressure. These changes may not only reflect brain ageing but may also contribute to pathological disorders, both AD and vascular cognitive impairment. Interaction of AD-type pathology with vascular changes may lower the threshold for the clinical appearance of cognitive decline.[10]

Neuropathological studies of ageing brain have focused on both positive and negative phenomena. Of the former, neurofibrillary pathology (neurofibrillary tangles, neuropil threads) and senile neuritic plaques, hallmarks of the AD brain, may be seen in cognitively normal older individuals. The development of neurofibrillary pathology follows a relatively stereotyped hierarchical pattern with age, appearing first in the transentorhinal cortex.[11] Spread to hippocampal and association cortex is associated with progressive appearance of cognitive decline. Senile plaques have a broader and more variable distribution; a significant burden may be associated with normal cognition. Negative phenomena include neuronal and synaptic loss. There is relative preservation of cortical and hippocampal neuronal populations with ageing, although subcortical structures such as the basal forebrain, locus ceruleus and substantia nigra do show neuronal losses.

What are the functional consequences of these changes? Typical cognitive ageing involves losses in processing speed, cognitive flexibility and the efficiency of working memory (or sustained attention). In other words, it may take more time and/or more trials to learn new information. Other cognitive domains, such as access to remotely learned information including semantic networks and retention of well-encoded new information, are spared with typical ageing. Hence impairments in these latter domains may be sensitive indicators of pathology rather than physiology.[12] Memory decline in healthy ageing may be secondary to a decline in processing speed and efficiency: controlling for processing speed may attenuate or eliminate age-related differences in memory performance, unlike the situation with memory impairment in dementia. Longitudinal studies of neuropsychological function, such as the Mayo's

Older Americans Normative Studies, indicate that there is considerable variability in normal older adults across different skills and consistency across different domains may not necessarily be observed.[12] Clearly this needs to be taken into account when assessing whether perceived cognitive decline is pathological or normal, that is, in defining neuropsychological norms for ageing. Likewise, norms may need to be age weighted rather than age corrected to detect cognitive impairment related to AD, the prevalence of which increases exponentially with increasing age. Many other situational influences may also impact on testing of cognitive skills, such as fatigue, emotional status, medication use and stress. These also need to be taken into account when considering the results of cognitive testing, as may factors such as educational and background experience. Many norms are also culturally-weighted.

Age-related cognitive decline may exist in individuals who do not fulfil validated criteria for the diagnosis of dementia or AD.[13] Various terms have been used over the years to describe this state, dating back to Krol's 'benign senescent forgetfulness' and including age-associated memory impairment (AAMI), age-associated cognitive decline (AACD), cognitive impairment, no dementia (CIND) and mild cognitive impairment (MCI). Some consensus has developed around the concept of MCI, criteria for which are the presence of a memory complaint, preferably corroborated by an informant; evidence of objective memory impairment for age and level of education; largely normal general cognitive function; essentially intact activities of daily living; and failure to fulfil criteria for dementia.[14] MCI is certainly a heterogeneous clinical entity, some examples of which certainly represent 'prodromal AD'. The annual conversion rate of MCI to AD is ~5–10%, such that most individuals with MCI do not progress to dementia even after 10 years of follow-up.[15] Updated diagnostic criteria for AD[16] seek to abolish the MCI category altogether in favour of an earlier, biologically based, diagnosis of AD, even without the clinical correlate of dementia which was insisted upon in earlier criteria.[13] This is logical if the hope is for earlier diagnosis and intervention to prevent cognitive decline to dementia. However, as yet no disease-modifying intervention has been discovered in the clinical arena, cholinesterase inhibitors proving robustly negative in trials aimed at slowing MCI to AD conversion and other interventions (blockers of amyloid production such as secretase inhibitors, immunotherapies to prevent amyloid deposition, tau aggregation inhibitors) remain at the clinical trial stage.

Since ageing *per se* is a significant risk factor for dementia, the ageing of the world population has important clinical, social and economic implications.[17] Primary and secondary prevention measures, perhaps facilitated by predicting risk of dementia in 20 years time based on factors such as age, education, blood pressure, cholesterol and obesity,[18] may be a more appropriate public health strategy, emphasizing a life-long, lifestyle approach to cognitive well-being.

Cranial nerves, including special senses

Olfaction (olfactory nerve; cranial nerve I)

Olfactory function diminishes with age, as does the sense of taste, which depends to a great extent on olfaction. Damage to the olfactory epithelium by pollutants or microbes is cumulative throughout life, affecting olfactory receptor neurones and cells further up the olfactory pathway. Impaired olfaction may also be an early sign of age-related disease, occurring in both Alzheimer's disease and Parkinson's disease. There is early involvement of the olfactory pathways by both neurofibrillary[11] and α-synuclein[19] pathology. Hence so-called age-related olfactory decline might in fact represent the early changes of a subclinical dementing disorder.[20]

Visual system: neuro-ophthalmology (optic, oculomotor, trochlear and abducens nerves; cranial nerves II, III, IV, VI)

Presbyopia is an age-related impairment of accommodation, attributed to increased rigidity of the lens, leading to hyperopia (far-sightedness). Age-related changes have also been documented in visual acuity, visual field, depth perception, contrast sensitivity, motion perception and perception of self-motion with reference to external space (optical flow). The pupils become progressively smaller ('senile miosis') and their reflex responses to light and accommodation become sluggish. Opacities in the lens and the vitreous may contribute to impaired visual acuity, including contrast sensitivity. Poor visual acuity may contribute to falls in the elderly. Whether photoreceptor loss from the retina may also be a factor in these changes is uncertain, but it may be relevant to diminished dark adaptation. Ocular changes such as cataracts and macular degeneration may obviously contribute to age-related visual impairment.[21]

Eye movements may become more restricted with age, particularly upward conjugate gaze (also observed in parkinsonism) and convergence. Bell's phenomenon, the reflex upward and outward deviation of the eyes in response to attempted forced closure of the eyelids, may be lost.

Other visual symptoms observed in ageing populations may reflect age-related neurodegenerative disease, for example the visual hallucinations of dementia with Lewy bodies (formed) or Creutzfeldt–Jakob disease (simple; Heidenhain variant) and the visual agnosia of Alzheimer's disease which may sometimes be the presenting feature (posterior cortical atrophy, visual variant of AD).

Hearing and balance (vestibulocochlear nerve; cranial nerve VIII)

Presbycusis is an age-related decline in hearing perception (i.e. increased auditory threshold), especially for mid-to-high frequencies and occurring bilaterally, which may also lead to reduced speech discrimination. It is believed to result primarily from loss of cochlear hair cells in the organ of Corti, although other structural changes in the auditory pathways may contribute, such as thickening of the basilar membrane, atrophy of the stria vascularis and degeneration of neurones in the spiral ganglion, cochlear nuclei and auditory centres in the brain. The latter may account for difficulties understanding speech which are greater than expected from audiometric thresholds *per se*.[22]

Age-related decline may occur in vestibular functions. Specifically, reductions in the ability to detect head position and motion in space, to elicit vestibulospinal reflexes which trigger automatic postural responses when the head position is changed and to solve sensory conflicts, are not uncommon. The neuroanatomical correlate may be loss of vestibular hair cells and nerve fibres and neuronal loss in the medial, lateral and inferior vestibular nuclei in the brainstem.

Sensorimotor function: motor systems

Appearance

A progressive loss of muscle bulk occurs with ageing, which is diffuse but most noticeable in intrinsic hand and foot muscles.[7] This is thought to be neurogenic, since electrophysiological studies show features of ongoing chronic partial denervation with compensatory reinnervation with ageing. Muscle fibres deprived of the trophic support of their innervating axons will atrophy.[1] Muscle biopsies in clinically normal elderly individuals confirm neurogenic change to be more apparent than myopathic change, with variation in fibre size (type I or types I and II fibre atrophy) and fibre type grouping suggestive of reinnervation. Degeneration of alpha motor neurones within the anterior (ventral) horns of the cervical and lumbar spinal cord is said to be the neuropathological correlate of these changes. However, fasciculations, a reliable sign of anterior horn cell disease, are not apparently a feature of normal ageing: if fasciculations reflect motor axonal instability due to recent reinnervation and collateral axonal sprouting, rather than an effect of denervation *per se*, then the electrophysiological and histological predominance of denervation over reinnervation might explain the absence of fasciculations in the elderly. The finding of fasciculations should therefore always prompt investigations for a pathological cause, such as motor neurone disease, compressive cervical radiculomyelopathy or multifocal motor neuropathy.

Tremor of the limbs and/or jaw has sometimes been given the label 'senile', since it is more prevalent in the elderly. The epithet conceals ignorance of the genesis of these signs. Limb tremor may be one feature of the extrapyramidal (parkinsonian) syndrome seen with increasing age in community-dwelling healthy individuals,[23] although the possible diagnosis of essential tremor should also be borne in mind, particularly if these tremors are worse with volitional activity. A diagnosis of essential tremor may have implications for therapy. Jaw tremor, often associated with the loss of teeth, has sometimes been labelled edentulous tremor. Tardive dyskinesia associated with previous neuroleptic use enters the differential diagnosis. Other movement disorders such as athetosis and chorea in the elderly have also been labelled 'senile',[7] but an attempt to ascertain an aetiological diagnosis should be made. Myoclonus, a common sign in advanced dementia, practically never occurs in normal old age.

Tone

Rigidity, an increase in resistance to passive movement around a joint which is constant throughout the range of joint displacement ('lead-pipe rigidity') and not related to the velocity of joint movement (cf. spasticity), is one feature of the extrapyramidal syndrome or parkinsonism. Akinesia, comprising bradykinesia (slowness in initiation and performance of movement) and hypokinesia (small amplitude of movements), is the defining and obligatory feature of parkinsonism. Tremor and postural abnormality, along with rigidity, may also occur as cardinal features of the syndrome of parkinsonism. A population based study of 467 individuals aged over 65 years in East Boston, USA, who underwent a structured neurological examination, found parkinsonism (defined as the presence of two or more of the following four signs: bradykinesia, gait disturbance, rigidity and tremor) in 159 individuals. The prevalence of parkinsonism increased with age.[23] The neuropathological correlate of these clinical findings may be the progressive spread of α-synuclein-immunopositive Lewy bodies and Lewy neurites, which have been reported in the brains of ageing but asymptomatic individuals.[19]

In addition to rigidity of extrapyramidal origin, another form of increased tone may be observed in older patients: 'superadded hypertonus of a quasi-volitional nature due to the patient's failure to relax as soon as his limbs are under examination'.[7] This clinical finding may be described as paratonia, paratonic rigidity or *gegenhalten*. The anatomical

correlate is bilateral frontal lobe pathology, most usually diffuse (small vessel) ischaemic cerebrovascular disease. Some authors classify paratonia as a release sign.[4]

Power

A meta-analysis investigating the relation between age and the prevalence of a variety of neurological signs, encompassing 50 studies involving 9996 individuals, found that the prevalence of decreased muscle strength did not rise with increasing age.[24] However, other authorities opine that decline in muscle strength appears progressively with ageing. Loss of muscle bulk (muscle wasting) is thought by some to be insufficient to explain the extent of weakness, although, as for wasting, neurogenic changes are thought to be the relevant neuroanatomical substrate. The oxidative capacity of exercising old muscle is reported to be less than that of young muscle. Strength may also be dependent on the integration of central mechanisms which may also be impaired with ageing due to loss of motor cortex cells, pruning of pyramidal cell dendritic trees and loss of synapses. Non-neurological factors such as age-related joint pain and deformity may contribute to an apparent loss of muscle power.

Coordination

Coordination refers to the rate, range, timing and direction of movement. Impairments in the speed of movement develop with advancing age, for example in hand or foot tapping. Activities of daily living such as dressing take more time in older individuals. These findings may reflect changes in muscle strength, the bradykinesia of the extrapyramidal syndrome (parkinsonism) which becomes more prevalent with age[23] or a combination of these. Cerebellar signs per se (finger–nose, heel–shin or gait ataxia) were noted to be rather uncommon in old age by Critchley.[7]

Reflexes

Phasic muscle stretch reflexes ('deep tendon reflexes')

The previously mentioned meta-analysis investigating the relation between age and the prevalence of a variety of neurological signs found that the prevalence of absent ankle reflexes was increased in healthy persons older than 60 years, although the majority (≥65%) retained their ankle jerks. The prevalence of absent knee, triceps or biceps reflexes did not rise with increasing age.[24] Variability of clinical findings may be related in part to the timing or method (plantar strike, Achilles tendon strike) of eliciting the ankle reflexes and whether reinforcement (Jendrassik manoeuvre) is performed. Furthermore, there is interobserver variation in the assessment of reflexes, with a biasing effect of prior clinical knowledge.[2]

Although typically regarded as part of the motor examination, the monosynaptic reflex arc encompasses both sensory and motor components. Both elements may be affected by age. Neurophysiological studies show not only a reduction in the amplitude of sensory nerve action potentials with ageing but also slowing of nerve conduction velocities, which reflect conduction in the large myelinated fibres that subserve the efferent limb of the monosynaptic reflex arc.

Superficial or cutaneous reflexes

Included within this rubric are abdominal reflexes, cremasteric reflexes (seldom examined) and plantar responses.

It is said that abdominal reflexes may become depressed with age *per se*, but other factors known to lead to their loss may contribute, such as obesity, previous abdominal surgery and a history of multiple pregnancies. Corticospinal pathway damage (upper motor neurone lesions) above T6 may lead to loss of all superficial abdominal reflexes, and lesions at or below T10 lead to selective loss of the lower reflexes with preservation of the upper and middle reflexes, in which case Beevor's sign (upward movement of the umbilicus in a supine patient attempting to flex the head on to the chest against the resistance of the examiner's hand) may also be present. All abdominal reflexes are preserved with cord lesions below T12. However, long tract signs in the legs are likely to be more obvious than abdominal reflex change with cord lesions at any level.[8]

Extension ('dorsiflexion') of the big toe when the lateral border of the foot is stroked with a blunt object, Babinski's sign, is deemed a reliable sign of upper motor neurone pathology other than in infants below about 24–36 months of age (hence this may also be regarded as a primitive or developmental reflex). No consistent changes have been documented with normal ageing,[25] although it is often difficult for even experienced practitioners to form a definite judgment on the plantar response and its reproducibility is also questionable.[3] Assessment of the response may be confounded by withdrawal of the foot in ticklish individuals. Differentiation from the striatal toe (tonic extension) seen in some parkinsonian syndromes is also important.

Primitive or developmental reflexes; 'frontal release' signs

A number of entities may be placed within this rubric of release signs,[4] including paratonia. The category may be further subdivided into prehensile and nociceptive reflexes;

the former includes the sucking reflex (tactile and visual), hand grasp reflex, foot grasp reflex (tonic foot response) and the rooting reflex; the last includes the snout reflex, glabellar (blink) reflex and palmomental (palm–chin) reflex. Corneomandibular and nuchocephalic responses are also described as primitive or developmental.[4]

Such reflexes may occur in normal individuals with ageing. For example, in a study of 2029 elderly volunteers aged 50–93 years, a significant increase in all the signs in patients over the age of 70 years was found,[26] and similar findings have been reported by others.[4] Of course, in the absence of longitudinal follow-up, it is possible that some of these 'control' patients may have had preclinical AD. Hence, although such signs occur more frequently in those with AD, their sensitivity and specificity for the diagnosis are poor.

Station and gait: postural responses

No neurological examination is complete without examination of the patient's gait, and this is particularly important in the elderly, since they are more prone to falls. Although some may be ascribed to pathological processes such as cervical myelopathy, Parkinson's disease or peripheral neuropathy, or to be due to environmental factors such as uneven floors, obstacles or poor lighting, many defy such explanation.

Walking has two major components, equilibrium (maintaining an upright posture) and locomotion (gait ignition and stepping). Changes in both functions occur with ageing. A framework to classify impaired gait in the elderly has been suggested.[27]

Maintaining balance while standing on one leg with the eyes closed shows significant change with ageing. Increased postural sway also occurs with ageing. Sway may be related to sensory impairments in the feet, particularly proprioception, with additional contributions from poor visual acuity and changes in vestibular function. Postural righting responses may be slowed and of reduced amplitude.

For the maintenance of static balance, somatosensory function is the most important system;[28] if impaired, reliance on visual function becomes more prominent. When both somatosensory and visual inputs are impaired, leaving vestibular function as the primary sense for balance control, difficulties are immediately apparent. Age-related changes in balance control subsystems are common, involving not only the sensory systems (somatosensory, visual and vestibular function), but also motor systems (strength, range of motion, coordination) and cognitive functions (sensory adaptation, attention), all of which may contribute to balance problems and falls in the elderly. However, such changes are neither inevitable nor irreversible, permitting the possibility of improvements in balance and mobility and a reduced incidence of falls in older adults.

Critchley's assertion that *marche à petits pas*, characterized by loss of elasticity, shortened steps and broadened base, was 'almost characteristic of healthy old age'[7] is no longer tenable, such changes now being thought to reflect pathological small vessel ischaemic cerebrovascular disease.[27] The changes in gait and stance more commonly seen with ageing are akin to those of parkinsonism, with slightly stooped posture, reduced arm swing and mild shortening of steps. In a community-based study of parkinsonism in the elderly, individuals with parkinsonism showed a twofold increased risk of death over a mean follow-up of 9.2 years and this was strongly related to gait disturbance.[23] Other gait disorders such as frontal gait disorder, cautious gait and isolated gait ignition failure (previously labelled gait apraxia) remain poorly understood but possibly reflect pathology within cortical motor pathways, perhaps in combination with other factors.

Sensorimotor function: sensory systems

Somatosensory function

A decrease in the sensitivity of vibratory perception is the most prominent age-related finding on sensory examination, particularly distally and more so in the legs than the arms. The previously mentioned meta-analysis investigating the relation between age and the prevalence of a variety of neurological signs found that the prevalence of absent vibration sense at the big toes or ankles increased in healthy persons older than 60 years although the majority ($\geq$65%) retained distal vibration sensation. In general, the prevalence of decreased pain or touch sense, absent vibration at the knees or fingers and decreased position sense did not rise with increasing age.[24]

Spatial acuity, as measured by two-point threshold measurement, may be reduced, especially distally. An increase in perceptual threshold for vibration, and also for thermal pain, may be found, whereas light touch tactile threshold is comparatively preserved.[28]

Distal degeneration of sensory axons is thought to be the neuroanatomical correlate of impaired distal sensation, reflected functionally in the reduction in amplitude of sensory nerve action potentials, with absence of sural responses in some individuals.[28] A reduction in sensory nerve conduction velocity may also be seen, although this is of course a relatively blunt instrument since it examines function in only the fastest conducting myelinated nerve fibres. Morphologically, ageing sural (i.e. sensory) nerves show a reduced density of myelinated and unmyelinated nerves and increased endoneurial collagen in individuals over the age of 60 years, in addition to changes indicative of nerve regeneration and degeneration and demyelination and remyelination. Ageing is also associated with reduplication of vascular basement membranes and thickening

of perineurial basement membranes.[29] These age-related changes may contribute to the cryptogenic sensory and sensorimotor neuropathies occurring in the elderly that tend not to progress rapidly and seldom lead to significant motor disability.[30]

Conclusion

The previous tendency to label cognitive, motor and sensory neurological changes occurring in the elderly as 'senile', implying a relationship to ageing *per se* and hence not requiring further elucidation, has been rightly replaced with a desire to search for aetiological explanations for such changes. Nonetheless, some common neurological signs occurring with ageing defy explanation and hence by exclusion may be labelled 'age related'. Undoubtedly, structural and functional changes occur within the nervous system with ageing and awareness of the consequent neurological signs will guide physicians in their appropriate management of these changes. The key skill which physicians must learn is to juxtapose a knowledge of the signs of normal ageing with those of incipient neurological disease.

Key points

- Ageing may have various meanings (successful, optimal, typical), which should be taken into account when considering which signs may be judged representative of 'normal' ageing.
- Ageing is associated with cognitive changes, specifically slower learning of new information and decline in delayed recall. These changes may reflect slowed processing speed and attentional function, rather than more rapid forgetting, and may be qualitatively different to the memory problems seen in pathological conditions such as Alzheimer's disease.
- The typical motor changes seen with ageing include distal muscle wasting and weakness, with diminution or loss of distal reflexes. The typical sensory changes seen with ageing include loss of distal vibratory sensibility; other modalities such as pain and proprioception may also be involved.

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CHAPTER 54

Sleep apnoea and sleep disorders

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Background

Prevalence

The prevalence of sleep problems in adulthood increases with age.[1–6] In the general population, the most common types of sleep problems reported are insomnia (difficulties in initiating and/or maintaining sleep) and early morning waking with an inability to return to sleep. By survey, half of elderly individuals report some extent of sleep difficulties, including trouble initiating sleep, poorer sleep efficiency, increased time in bed, more night-time awakenings, earlier wake-up times and more daytime naps.[7] Older adults primarily report difficulty in maintaining sleep and, although not all sleep changes are pathological in later life, severe sleep disturbances may lead to depression (see below), cognitive impairments and stress to partners.[2,8]

Insomnia is supposedly the most prevalent sleep disturbance in the elderly, with up to 40–50% of those aged over 60 years reporting difficulty sleeping,[5] with an annual incidence rate of 5% in those over 65 years old.[9] General prevalence rates of insomnia in people aged 65 years and over are reported to range between 12 and 40%.[10] Interestingly, prevalence rates of insomnia are higher when coexisting medical or psychiatric illness is taken into account.[1,11,12] Foley *et al*.[9] reported that only 7% of the incident cases of insomnia in the elderly occur without a comorbid condition. Furthermore, lifestyle changes related to retirement, the increased incidence of health problems and the use of medication all place older people at increased risk of disrupted sleep.[13] The relationship between sleep problems and depression in the elderly is strong, but prone to confounding influences.[1] Sleep disturbances may also be comorbid with (but not necessarily causative of) dementia, while Alzheimer-related deterioration of suprachiasmatic nucleus neurons could cause still further disturbance in sleep–wake cycle disorders.[14]

Basic issues concerning sleep in the elderly

In spite of the high prevalence of sleep disorders in the elderly, relatively little is known about them. This may be because gerontologists, in common with many other clinicians, are taught very little about sleep at either undergraduate or postgraduate levels.[15–18]

In short, sleep is a reversible state of reduced awareness of and responsiveness to the environment, which usually occurs when lying down quietly with little movement. The functions of sleep are still being debated, with a range of theories postulating physical and psychological restoration and recovery, energy conservation and a range of biological purposes. No single theory encapsulates all of these functions, and it is likely that sleep serves many purposes. For most people, a significant lack of sleep impairs both physical and psychological functioning.

Sleep problems may relate to the quality, duration or timing of sleep. Asking patients whether they feel sleepy during the day, whether they feel refreshed in the morning and whether they are sleeping at socially appropriate times provides good indicators of whether these important aspects of sleep are acceptable.

There are essentially three main sleep problems: too much, too little and the so-called *parasomnia*s (things that go bump in the night!). However, the *International Classification of Sleep Disorders*, 2nd edition,[19] lists more than 80 sleep disorders. This chapter focuses on the most common sleep disorders faced by people aged over 65 years and considers diagnostic and treatment issues relevant to each of them.

A variety of factors may give rise to the sleep problems reported (and often under-reported) by the elderly.[2,20] Principally, these are: medical illnesses, both chronic and acute; the effects of medication; psychiatric problems; primary sleep disorders; social changes; and behaviour patterns that are not conducive to good sleep. These problems may

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be exacerbated by poor handling of these problems by the patient, his or her family, doctors and other healthcare workers.

The consequences of sleep problems can be serious and costly. Lack of sleep and sedative medications have been shown to be associated with falls and accidents.[21–24] The risk of medication side effects and complications related to surgery could also be detrimental in the elderly population.[25] Sleep-related breathing problems, or sleep apnoea, have serious cardiovascular, pulmonary and central nervous system (CNS) effects.[26] In patients with dementia, sleep disorders frequently lead to nursing home placement. Experimental studies of total sleep loss indicate that this is associated with a negative impact on mood and cognitive functioning, although as with most sleep problems, individual variations can be substantial. For ethical reasons, the number of studies in this area is limited. Partial sleep loss has been better researched and these studies are likely to be more relevant to daily life and clinical practice. A loss of sleep of between 1 and 2 h per night has been shown to lead to irritability and poor concentration. When sleep loss is prolonged, disorientation, hallucinations and inappropriate behaviour may be reported.[27–31] It is important that sleep disorders are diagnosed properly and treated accordingly in view of their consequences to patients and also carers. These problems also impact healthcare costs,[32] further justifying medical attention. Table 54.1 gives a brief guide to these problems and their treatments.

Sleep structure

Normal sleep consists of a number of stages that can be simplified into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. REM sleep is generally associated with dreaming together with lability of heart rate, blood pressure and respiration. Brain metabolism is highest in this stage of sleep, with a low-voltage, mixed-frequency non-α electroencephalogram (EEG). Spontaneous rapid eye movements are seen and skeletal muscle tone is virtually absent. REM sleep makes up ~25% of total sleep time in adults and it is when most dreaming occurs. REM sleep episodes occur in ~90 min cycles, with each episode increasing in duration as the night progresses. It is sometimes known as paradoxical sleep since the EEG is most like wakefulness and yet there is very little physical activity.

NREM sleep is subdivided into four stages of increasing depth and dominates the first half of a normal night. Stage 1 occurs at sleep onset or following arousal from another stage of sleep. The EEG is of low voltage with mixed frequencies and reduced α-activity compared with the awake state. It makes up ~5% of the total sleep time. Stage 2 contains more slow-wave activity and sleep spindles and K complexes are seen. It makes up ~50% of overnight sleep. Stage 3, also about 5% of sleep time, is yet more slow-wave EEG activity and stage 4 is the slowest activity and makes up ~15% of sleep. Together, stages 3 and 4 are known as slow-wave sleep. These are the deepest forms of sleep from which awakening is especially difficult. Arousal disorders such as sleep-walking and confusional arousals arise

Table 54.1 Common sleep problems and their treatments in the elderly.

Sleep disorder	Clinical features	Diagnostic method	Treatment	Comments
Sleep apnoea	Reports of stopping breathing for short periods during sleep; daytime sleepiness; loud snoring; obesity	History; physical examination; polysomnography	CPAP; weight loss	Intermittent airway closure; more common in men; sedatives unhelpful
Restless legs syndrome	Motor restlessness; pacing at night	History	Dopaminergics; benzodiazepines	More common with iron deficiency; PLMD often also present
Periodic limb movement disorder	Legs kicking in sleep; arousals from sleep; daytime sleepiness	Polysomnography	Dopaminergics	May extend to other muscle groups; may occur during wakefulness also
REM sleep behaviour disorder	Apparent acting-out of dreams	History and polysomnography	Clonazepam	Mostly idiopathic; injury to bed-partner should be considered
Advanced sleep phase	Falling asleep and waking too early	History/diary (with actigraphy)	Psychological; bright light; (melatonin)	More common in institutionalized elderly
The insomnias	Difficulty initiating or maintaining sleep	History/diary (with actigraphy)	Psychological; medication (for acute insomnia only)	Consider the type of insomnia with medication

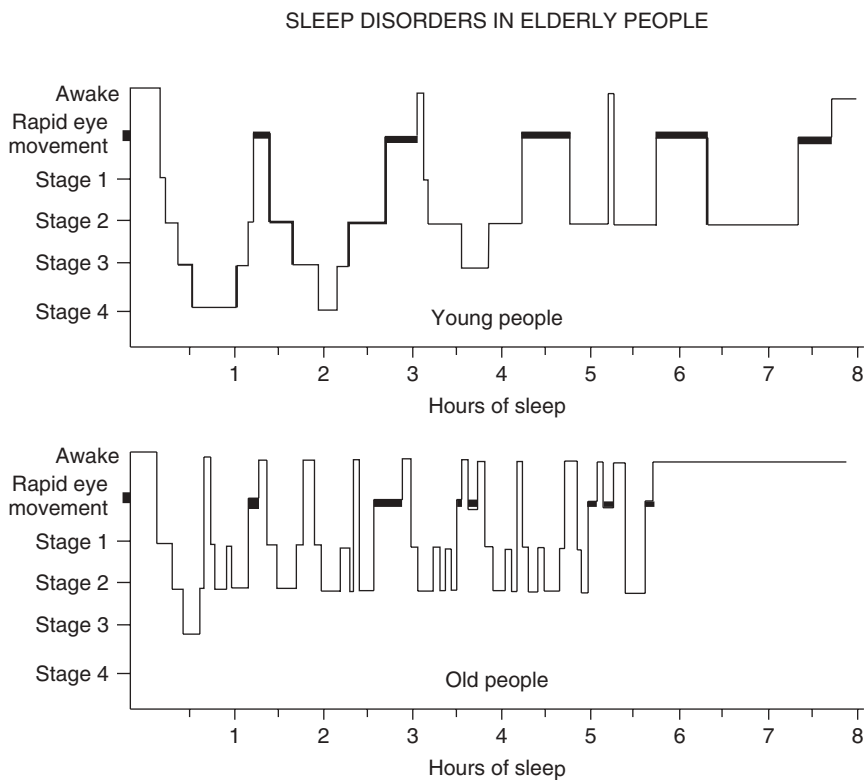

Figure 54.1 Sleep hypnogram for a young adult and an 80-year-old. Horizontal axis = time; vertical axis = sleep stage. These subjects fall from wakefulness into slow-wave non-REM sleep in stages 1–4 before their first REM phase where most dreaming occurs. The first half of the night is dominated by slow-wave sleep and the second half by REM sleep. Thus, a patient who is limiting their sleep is more likely to be deficient in REM sleep and, therefore, more likely to have cognitive difficulties. Note the shorter, more fragmented sleep in the elderly compared with the young adult.

in slow-wave sleep. These sleep stages are summarized in Figure 54.1, which shows a summative hypnogram for a 25-year-old adult and an otherwise healthy 80-year-old person for comparison.

The most striking differences are that the younger person sleeps for a longer time, with fewer wakes during the night. The elderly person sleeps less and this sleep is highly fragmented with many arousals, some of which are for a considerable time. The older person also has very much less deep NREM sleep. Whether the older person needs less sleep at night or simply cannot get it is not currently known, but it may go some way in explaining why high levels of daytime sleepiness in the elderly is so common.[2] Overall, it can be seen that sleep efficiency (the ratio of time asleep to time in bed) has fallen. The reduction in deep sleep and its replacement with lighter stage 2 sleep is of clinical significance as it is reflected in perception of sleep quality.[33]

The noise threshold required to waken an older person appears to be lower than in younger adults despite reductions in hearing sensitivity,[34] although a study looking at this issue in people living near Heathrow Airport indicated that bed-partner behaviour was more influential than noise.[35] Perhaps the elderly have a general increase in sensitivity to external stimuli, which decreases sleep quality.

Whether these sleep problems are related to gender is not yet properly understood. It appears that women report more sleep problems, although men have objectively more disordered sleep. This may be due to women reporting their sleep problems more frequently.[36]

The timing of sleep in the elderly is often phase advanced, that is, they generally go to sleep early and wake up earlier than they would like. The early morning waking may lead to sleep deprivation and excessive daytime sleepiness. Conversely, some older people may develop a phase delay, that is, becoming 'night owls' with bedtime delayed until late. This behaviour may have been accommodated in youth when the cues of bright morning light and other environmental influences were stronger; however, deterioration of light perception has weakened these cues. These patients may go on to develop very irregular sleep–wake cycles, which can be difficult to treat.

Dementia

Dementia presents additional challenges to physicians because many of the sleep changes seen in the normal ageing population are amplified. Compared with controls, older people with dementia have a longer sleep latency (time between going to bed and getting to sleep), wake up in the night more frequently and for longer periods and are more likely to fall asleep during the day.[37–39] Circadian rhythm problems are also more common and 10% of older people with dementia actually sleep more

during the day than during the night. These changes are often accompanied by episodes of night-time agitation and sundowning, which are among the most common reasons for admission to a nursing home.[40] While there is some evidence of a possible link between sleep problems and dementia,[37] individual differences are great and do not discriminate effectively between dementia and non-dementia patients. The possible causal mechanism is thought to include a degeneration of the neurons in the suprachiasmatic nuclei. Whatever the organic origin, it is likely that behavioural factors will influence sleep problems. There is good evidence that a regular day–night pattern of activity with minimal naps and optimal daytime stimulation is helpful. An exhausted carer leaving their demented relative to sleep during the day in order to give themselves a much-needed break may make life considerably worse in both the short and medium term.

Sleep disturbances in the elderly with dementia should be treated according to the specific disorder and symptom.[7]

Institutionalization

The link between institutionalized living and sleep disturbance is perhaps best demonstrated by the high levels of hypnotic drug consumption that have been found in hospitals and nursing homes.[41] Within these institutions, sleep disturbance may be related to the act of admission itself. A period of adjustment may be required (3–4 days), as is common in many other settings where people do not sleep normally when their usual night-time environment changes. Hypnotics should not be prescribed for people who cannot sleep in a new institution unless they also have other problems. Moving to an institution is likely to be contemporaneous with a life event such as the death of a partner, discomfort or pain, any of which may have a negative effect on sleep. Noise has been shown to be a significant factor in the sleep of the institutionalized elderly and, often, noise levels in such homes are excessive. Institutions that fail to stimulate residents during the day and that have routines that are not conducive to sleep may be more likely to have sleep-disordered residents.

Assessment

As sleep can be influenced by medical conditions, chronic diseases, psychiatric disorders, medications and a host of other conditions, the first step in treating sleep disturbances in the elderly is to identify or assess the underlying problem.[42] Subjective enquiries about the sleep of elderly patients should be made routinely as they are at special risk of sleep disorders, which they tend to under-report and see as normal and untreatable. More detail on the assessment of sleep disorders can be found elsewhere.[43]

All patients should be screened by being asked whether they sleep enough and whether their sleep is of good quality. They should be asked if they are sleepy during the day and whether their nocturnal sleep is disturbed at all. Information may be corroborated by carers or bed-partners. If any of these enquiries are positive, a fuller sleep history should be taken. This should include details of the nature of the sleep complaint, its onset and so on. Contributing factors and patterns of occurrence should be explored. The impacts of both sleep problems and previous treatments on patients and their families should be assessed. Patients should be taken through their 24 h schedules, which may elicit helpful information about timing and other aspects of their sleep. If justified, clinicians may then consider giving patients sleep diaries to complete. Sleep diaries can be helpful in understanding the times a patient goes to bed, gets to sleep, wakes in the night, wakes in the morning and gets up. Using sleep diaries, estimates can be made of sleep latency and efficiency (times between getting to bed and getting to sleep and ratio of time asleep to time in bed, respectively). There are many versions of sleep diaries available (for an example, see http://science.education.nih.gov/supplements/nih3/sleep/guide/nih_sleep_masters.pdf), but it may be helpful to customize one to attend to the particularly relevant points raised in the clinical interview. An example diary is given as Figure 54.2.

From the physical examination, attention should be paid to any systemic illness, including cardiorespiratory disease or neurological disorder such as Parkinson's disease or stroke, which may disturb sleep. Obesity or craniofacial abnormalities may suggest upper airway obstruction and any psychiatric problems (particularly depression and anxiety) should be noted during the physical examination.

Objective investigations of sleep are not justified for all sleep disorders.[44] The main indications for them are sleep apnoea, narcolepsy or periodic limb movements (PLMs). If details of parasomnias (such as REM-sleep behaviour

Day of the week	Example day
When did you rise from bed this morning?	8 a.m.
What time did you get into bed last night?	Midnight
How long did it take you to fall asleep? (min)	45 min
How many times did you wake during the night?	3
How long was each wake during the night? (mins)	10, 10, 20
How long did you sleep altogether? (h min)	6 h 35 min
How much alcohol (if any) did you drink last night?	1 glass wine
How many sleeping pills, if any, did you take to help you sleep last night?	None
How much caffeine did you consume yesterday? (tea, coffee, coke etc.)	2 cappuccinos, 1 tin Coke

Figure 54.2 Sleep diary.

disorder) are unclear from clinical interview, an objective check on the clinical impression is required. Generally, objective investigation is in the form of polysomnography (PSG) in a sleep laboratory, although home PSG is becoming better established and validated. When this is more accepted and widely available, home PSG may diminish the so-called *first night effect*, which is common when patients spend their first night in a sleep laboratory. PSG studies should include an EEG, an electrooculogram and an electromyogram in order to compile an overnight hypnogram such as in Figure 54.1.

Commonly, PSG is extended to include respiratory variables where sleep-related breathing disorders (SRBD) are suspected and anterior tibialis electromyogram if period limb movements of restless leg syndrome (RLS) are suspected.

Alternative objective measurements of sleep can be made using actigraphy, small wristwatch-sized motion detectors that distinguish wake and sleep and so are useful for circadian rhythm disorders and insomnia.[45]

Diagnosis and treatment

In general, current evidence indicates that non-pharmacological treatments, such as cognitive behavioural therapy (CBT) or sleep education, are more effective in the treatment of sleep disturbances in the elderly.[23,25,46] Bright light therapy and physical exercise have also been shown to be effective in improving sleep outcomes in the elderly.[47,48] Although some evidence supports the use of pharmacology in the treatment of selected sleep disorders, most studies are limited by small, mixed samples and short trial periods of a few days.[23] The most prevalent sleep disorders and their relative treatment options will be considered in greater detail here.

Apnoea, sleep-related breathing disorders (SRBD)

The most common sleep-related breathing problems are apnoeas (temporary cessations of breathing) and hypopnoeas (a form of shallow rapid breathing). They can be due to an occlusion of the airway (obstructive sleep apnoea) or reduced respiratory drive (central sleep apnoea). The most obvious features of these are stopping of breathing followed by gasps for breath during sleep episodes and excessive daytime sleepiness, both of which increase with age. These events can occur hundreds of times each night and commonly impair daytime functioning significantly because the patient is aroused during each episode and is, therefore, deprived of sleep and deep NREM sleep. The main risk factors for apnoea are male gender and obesity.

The clinical importance of SRBD is substantially demonstrated by numerous studies over the past 30 years. The presence of five or more apnoeic episodes per hour is generally considered pathological. It has been reported that one in 10 adults aged between 30 and 60 years stops breathing 10 or more times per hour, whereas 60% of people aged over 65 years do this.[49,50] The reasons for this may be due to the elderly having physiological changes such as longer soft palates, larger pharyngeal fat pads and lower response of genioglossal muscle to negative pressure stimulation.[51] An Australian study[52] reported that 72% of patients with dementia had clinically significant apnoea (>5 events per hour) compared with 46% of controls. Oxygen desaturation experienced during apnoeas may compromise neuropsychological functioning in dementing illness, although reports of this vary in the literature.[53] Sleep apnoea patients who also have congestive heart failure have a mean survival time of less than 2.71 years compared with 4.04 years in patients with congestive heart failure alone.[54]

Patients suspected of having sleep apnoea may be evaluated in a sleep laboratory where monitoring of the electroencephalogram, blood oxygen saturation, airflow and chest and abdomen respiratory efforts can be performed to confirm the diagnosis.

The treatments of choice for sleep apnoea are continuous positive airways pressure (CPAP), which requires a device that pushes air into the airway to keep it open at night, positive airway pressure (PAP) therapy, bilevel PAP, autotitrating CPAP or autotitrating bilevel PAP.[55] These devices have been found acceptable in older patients, including those with mild Alzheimer's disease. In this latter group, snoring and daytime sleepiness were reduced; depressive symptoms in both patients and carers improved.

Oral appliances that move the mandible forward or pull the tongue forward during the night may also be used to treat sleep apnoea. However, these do not always work well with dentures and may not be appropriate for all older adults. Avoiding alcohol and hypnotics can be helpful as these are respiratory depressants. Weight loss may be an effective intervention since obesity is one of the biggest predictors of apnoea. Changing sleep position from the back to the side can be effective if it can be shown that the apnoeas occur only when patients sleep on their backs. Surgical interventions are not usually recommended because of the possible risks and complications.

Periodic limb movements in sleep (PLMs) and restless leg syndrome (RLS)

PLMs is a condition in which the legs kick or jerk for between 0.5 and 5 s at 4–90 s intervals throughout the night. PLMs causes fragmented sleep (especially the loss of deeper slow-wave sleep) and patients report insomnia and excessive daytime sleepiness. This idiopathic disorder also increases with increasing age,[56] with prevalence among

elderly people living at home at about 45% and with the prevalence of restless leg syndrome in older adults almost doubling from its 10% prevalence in younger adults.[57,58] However, not all people with PLMs experience disturbed sleep, although the quality of their sleep can be greatly impaired by this disorder, which usually comes to light from partner complaints.

RLS is a related disorder where patients experience irritating 'creepy–crawly' leg sensations that are relieved only by moving the legs. It can occur prior to sleep onset and in the daytime when the person is relaxed. RLS can significantly interfere with the onset of sleep. Risk factors for both PLMs and RLS include not only increasing age but also renal failure and iron deficiency (serum ferritin level $<50\,n\,ml^{-1}$). Both disorders can be diagnosed from patient and partner reports of these clinical symptoms and confirmed by electromyography in a sleep laboratory if necessary.

Both PLMs and RLS can be treated with medication, usually carbidopa–levodopa (25–100 mg) and other dopaminergic agents. Comorbid low iron level may need to be corrected for a satisfactory response. Pergolide, at a very low dose (0.05–0.5 mg), has also been used for these disorders. Some patients report that soaking the legs and feet in a warm bath or taking regular exercise provides some relief.

REM-sleep behaviour disorder (RBD)

REM-sleep behaviour disorder is a rare condition that occurs mostly in the elderly and primarily in men.[59,60] In patients with RBD, muscle tone is preserved in REM sleep; patients may be able to act out their dreams. In suspected cases, patients should be seen urgently because they risk harming themselves and those around them. Treatment at bedtime with a low dose of a long-acting benzodiazepine such as clonazepam is generally effective. Clonzapem has been shown in non-randomized trials to result in partial or complete cessation of abnormal nocturnal motor movements in 90% of patients.[61]

Circadian rhythm disorders

In adults with normal circadian rhythms, sleepiness occurs at around 11 p.m. and persists for around 8 h. This period is associated with a decrease in core body temperature, which is thought to be a cause of sleepiness. These cycles are thought to be related to changes in the levels of light. As ageing occurs, the circadian rhythm seems to advance so that sleepiness occurs earlier in the evening and morning waking occurs correspondingly earlier. Most older adults try to stay awake even though they feel sleepy in the early part of the evening. However, they still wake up earlier as their core body temperature rises, leading to sleep deficiency and excessive daytime sleepiness and/or naps during the day. Some elderly people doze off in the early evening, have sleep onset problems at bedtime and wake early; this cycle may impair their daytime functioning still further. These sleep phase problems are common in many groups of patients, notably visually impaired people, and treatment of these problems can be difficult as these dysfunctional patterns of sleep can become entrenched.

Treatment of advanced sleep phase (sleeping too early) involves delaying the sleep cycle. Strong social and environmental cues such as meals at regular times, exposure to light and exercise are most important. This may be accomplished artificially using bright light, although evidence for this intervention is limited in patients both with and without dementia.[47] Usually, a light source of at least 10 000 lux (which is far greater than is normal indoors) should be used late in the day (say 4 p.m.). Light exposure may delay the circadian rhythm so patients become sleepy later in the evening and sleep later in the morning, also improving their sleep continuity. Both healthy community-living older adults and nursing home patients have been found to delay their circadian rhythms successfully and improve their wake–sleep cycle through evening light exposure.[62,63] If patients continue to wake early and want to go outdoors, they should be encouraged to wear sunglasses lest the early light exposure shifts their sleep phase still earlier. Bright light treatment is, however, contraindicated in patients with mania. Alternative treatments include melatonin, which is a hormone released by the pineal gland. Convincing research evidence here is even more limited. There is little consensus regarding effective dosage, but some studies purport that melatonin replacement therapy may also improve sleep efficiency in the elderly.[64–67] An intervention employing bright light therapy and melatonin treatment has also been tested in elderly patients with dementia and shown to improve some cognitive and non-cognitive symptoms of dementia and also sleep efficiency.[68] According to systematic review and meta-analysis, the short-term use of melatonin is not effective in treating most primary sleep disorders, but may be effective in treating delayed sleep phase syndrome and circadian rhythm disorders.[69] As there is no evidence regarding the safety of long-term use, however, clinicians should exercise caution in its prescription.

The insomnias

According to a recent cross-sectional study of prevalence, primary insomnia affects approximately one-fifth of people over the age of 65 years. It is also more frequent in females and related to the coexistence of other health problems, medication and inadequate sleep hygiene.[70] The

International Classification of Sleep Disorders[19] defines 11 subtypes of insomnia, that is, disorders of initiating or maintaining sleep. However, in day-to-day practice, the technology required to diagnose each of them precisely limits the value of this system. It is, nevertheless, important to consider the type of insomnia with which the patient presents. The main types are psychophysiological insomnia (with psychosomatic arousal, excessive concern about sleep adequacy and somatized tension), inadequate sleep hygiene (where the sleep problem appears to be caused or maintained by dysfunctional practices around sleep) and sleep-state misperception (where the insomnia diagnosis is not supported by objective findings).

A wide range of medical conditions is associated with the insomnias, including arthritis and cancer. Neurological problems such as dementia, RLS and Parkinson's disease are also associated with it and, in the elderly, congestive heart failure, asthma, gastroesophageal reflux, urinary incontinence, nocturia and benign prostatic hyperplasia are commonly comorbid with insomnia. Depression is strongly linked with insomnia in both directions, that is, as both cause and effect. Anxiety disorders, prevalent in the elderly, may in part be caused by bereavement, social changes and relocation, but insomnia is associated with all of them. Overall, about 20% of patients with insomnia have depression and about 90% of patients with depression report a sleep disturbance.[7] There are several drugs that cause insomnia, including alcohol, nicotine, CNS stimulants, β-blockers, corticosteroids, bronchodilators, calcium channel blockers and thyroid hormones. Alcohol is often used to induce sleep, but its effect is short-lived and leads to early waking. Adjusting the dose or time of day when medications are taken can improve a patient's insomnia; for example, wake-promoting drugs could be taken earlier in the day and sedating drugs later.

Evaluation of insomnia should be based on a good sleep history, augmented by a sleep diary and a physical examination. Initially, medical and psychiatric problems should receive attention and, if the insomnia remains, identification of an underlying cause should be attempted before direct treatment for insomnia is indicated. Non-pharmacological treatments such as sleep hygiene and education integrated into a cognitive behavioural framework have been shown to be effective in the treatment of insomnia[10,71] and should be considered first for chronic insomnia to reduce polypharmacy especially in view of the other drugs commonly taken by the elderly.[46] Sleep hygiene should aim to establish: regular sleep and wake times; avoidance of excessive time in bed awake (sleep restriction); stimulus control in the form of a clear routine leading up to sleep; daily activity and exercise; appropriate use of caffeine (avoidance after 4 p.m.); limited alcohol and nicotine use; and elimination of loud noise, excessive light and uncomfortable room temperature. Inaccurate attributions should be challenged and corrected about what sleep is, how common problems can be and how sleep changes with age. Even if poor sleep habits are not responsible for insomnia, the elimination of such habits will avoid their role in the maintenance of the problem.

There is some evidence from other populations that written information can be an effective way of delivering these sorts of treatments, although no good trials have been conducted with the elderly.[72] Further studies with other populations have shown that the concurrent treatment of comorbid conditions (i.e. depression and insomnia) can lead to better overall response.[73] Cognitive behavioural intervention for insomnia includes stimulus control, aiming to set up conditions conducive to sleep for the patient. It typically involves removing any sleep-incompatible stimuli from the bedroom and the patient is told to get up if not asleep within 20 min of getting into bed. It is essentially a conditioning treatment that develops strong associations between the bedroom and sleep while extinguishing associations between sleep and any other place. CBT, in the treatment of insomnia, has been shown to be equally effective as pharmacology with better long-term outcomes,[10,23,74,75] and also to improve pharmacological outcomes.[76] As such, CBT has been deemed the most effective treatment for insomnia.[71].

Sleep restriction limits the amount of sleep to the length of time that the person is likely to sleep. It aims to improve sleep efficiency (ratio of time asleep to time in bed) by either increasing time asleep or reducing time in bed. Most patients want to increase their time in bed, even though this may not be physiologically necessary. By asking patients to use a sleep diary carefully, sleep efficiency can be calculated and sleep compressed and, if necessary, expanded later provided that efficiency is maintained. It can be difficult to persuade elderly patients to accept this treatment as it is based on a key time when they must get up, however little sleep they may have had. In this way, their increasing tiredness will increase the drive for sleep.

Other cognitive behavioural techniques currently with less (although increasing) research evidence to support them include imagery and relaxation, paradoxical intention and thought suppression. Daily exercise is thought to be important in promoting good sleep, although firm evidence for it is again limited.[48]

In acute insomnia, some patients may benefit from short-term use of sleep-promoting medications.[77] Over-the-counter antihistamines should be used with caution because of their long duration of action and their anticholinergic effects in the elderly. These may cause confusion, constipation and urinary retention.[78] Furthermore, the NIH 71

Table 54.2 Common pharmacological options.

Agent	Dose/timing	Comments
Non-benzodiazepine hypnotics		
Zolpidem tartrate (Ambien)	5–10 mg at bedtime	Can be used for sleep-onset and maintenance insomnia (as half-life is 1.5–4.5 h)
Zaleplon (Sonata)	5–10 mg at bedtime	Can be used for sleep-onset and maintenance insomnia (as half-life is 1 h)
Benzodiazepines		
Temazepam (Restoril)	7.5 mg	Exclude obstructive sleep apnoea before prescribing
Antidepressants for insomnia and depression		
Sertraline.HCl (Zoloft)	50 mg in the morning	Well tolerated
Fluoxetine.HCl (Sarafem)	20 mg in the morning	As for sertraline; however, consider lower doses in patients over 65 years old with concurrent disease or multiple medications
Mirtazepine	15 mg at bedtime	For use with depression and severe insomnia and anxiety

conference concluded that owing to the lack of systematic evidence and the potential risk of adverse effects, the use of antihistamines is not recommended, particularly for older adults. Among the hypnotics, the treatment of choice is a short-acting benzodiazepine receptor agonist. Short-term use and low doses are recommended.[79] Occasional use reduces the possibility of withdrawal effects. The option to use such a drug may reduce anxiety about sleep in the patient and therefore be beneficial. In cases of excessive daytime sleepiness, referral to a sleep specialist is indicated, as this symptom can be dangerous.

The choice of sedative–hypnotic agent for insomnia should be based on issues of efficacy, including whether it consolidates fragmented sleep, whether it can be administered at different times in the night and the effect on next-day functioning. Thus, a short half-life with few withdrawal symptoms and minimal adverse events with no tolerance should be key considerations. Some common options are listed in Table 54.2.

It should be stressed that among a physician's first set of treatment goals should be the improvement of sleep hygiene in the patient, moving on to drug treatment only if this proves insufficient. The following drug treatments have been shown to be effective in older adults with a low propensity for causing withdrawal, dependence, tolerance or clinical residual effect: the newer selective short-acting type-1 GABA benzodiazepine receptor agonists (BzRAs), including zolpidem[80–82] and zaleplon.[83,84] The primary effects involve decreasing sleep onset time and/or increasing total sleep time.

Key points

- It is necessary to ask directly about sleep problems lest they go unnoticed and untreated. Carefully considered sleep diaries and histories are essential diagnostic tools in this area.
- Non-pharmacological interventions such as sleep hygiene and cognitive behavioural treatments should be considered first.
- In dementia, encouraging a regular schedule including exercise and light meals (especially later in the day) but excluding alcohol and caffeine in the evening is helpful.
- Comorbid problems such as pain or depression and current medications should be considered as possible causes.
- Short half-life medications such as zolpidem and zaleplon may be considered for short-term use.

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CHAPTER 55

Headache

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Introduction

The International Headache Society (IHS) classification, ICHD-II,[1] divides headaches into two broad categories: primary and secondary headache disorders. Secondary headaches are attributed to another disease and can be caused by intracranial or extracranial structural abnormalities or by systemic or metabolic conditions. In the primary headache disorders, the headache itself is the illness (Table 55.1). The primary headache disorders include migraine, tension-type headache (TTH) and trigeminal autonomic cephalalgias (including cluster headache). Migraine is further subdivided into two groups: migraine with and without aura. TTH is subclassified as either episodic tension-type headache (ETTH) or chronic tension-type headache (CTTH). Cluster headache is similarly divided into the episodic and chronic varieties. Chronic daily headache (CDH), a term in common use, is subclassified into CTTH, chronic migraine (CM), hemicrania continua (HC) and new daily persistent headache (NDPH), and is often associated with acute medication overuse.

Headache prevalence is age dependent. Migraine prevalence peaks near age 40 years and declines afterward (Figure 55.1). With ageing, not only is there a change in prevalence of the primary headache disorder but also a shift to new or organic causes of headache.[2] Migraine incidence and prevalence decrease, whereas brain tumours, subdural haematomas and other structural causes of headache increase. Elderly patients have more comorbid medical illness and some headache disorders, such as giant cell arteritis (GCA), occur principally in the elderly (Table 55.2).

Headache is common in the elderly. The 1 year prevalence of headache in an elderly Italian population (aged 55–94 years) was 40.5%; TTH 45.8%, migraine headache 5.7% and trigeminal neuralgia 1.6% In this population, headaches caused significant impairment of health-related quality of life.[3] The complaint of 'frequent headache' was found in 11% of elderly women and 5% of elderly men participating in a health screening programme; however, these patients were commonly found to have other diseases or somatic or psychological symptoms.[2] These facts justify a lowered threshold for ordering tests when older patients present with headache, particularly if the headaches are of recent onset, are atypical or are associated with neurological findings. Headaches that begin after age 65 years are more often secondary.

The evaluation of the elderly patient with headache must be directed to rule out serious secondary causes of headache such as tumour, subdural haematoma, stroke, transient ischaemic attack and giant cell arteritis. In the elderly patient, when the diagnosis is not obvious, neuroimaging and a sedimentation rate should be considered[2] (Table 55.3). In this chapter, we discuss the primary headache disorders as they relate to the older patient, some of the more important secondary headache disorders and finally cranial neuralgias.

Diagnosis and clinical description of headaches

The criteria for headache diagnosis were updated by the IHS in 2004.[1] The first step in establishing a diagnosis is a complete history, which should include the following information: the age at headache onset; the time of onset (day, season); the location, severity and type of pain; the attack frequency (including any change in frequency); associated symptoms; precipitating and relieving factors; the patient's sleep habits; and the family history. In addition, a complete medication history should be taken to evaluate the doses, duration of use and effectiveness of previous headache medications, and also to determine if any medications that could exacerbate headaches are being used or overused.

The patient should keep a diary to record any changes in headache between office visits, especially if medication was modified. A diary will make the patient more aware of the disease process and also help the physician to evaluate

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 55.1 IHS migraine classification.

1 Migraine
- 1.1 Migraine without aura
- 1.2 Migraine with aura
  - 1.2.1 Typical aura with migraine headache
  - 1.2.2 Typical aura with non-migraine headache
  - 1.2.3 Typical aura without headache
  - 1.2.4 Familial hemiplegic migraine (FHM)
  - 1.2.5 Sporadic hemiplegic migraine
  - 1.2.6 Basilar-type migraine
- 1.3 Childhood periodic syndromes that are commonly precursors of migraine
  - 1.3.1 Cyclical vomiting
  - 1.3.2 Abdominal migraine
  - 1.3.3 Benign paroxysmal vertigo of childhood
- 1.4 Retinal migraine
- 1.5 Complications of migraine
  - 1.5.1 Chronic migraine
  - 1.5.2 Status migrainosus
  - 1.5.3 Persistent aura without infarction
  - 1.5.4 Migrainous infarction
  - 1.5.5 Migraine-triggered seizures
- 1.6 Probable migraine
  - 1.6.1 Probable migraine without aura
  - 1.6.2 Probable migraine with aura
  - 1.6.5 Probable chronic migraine

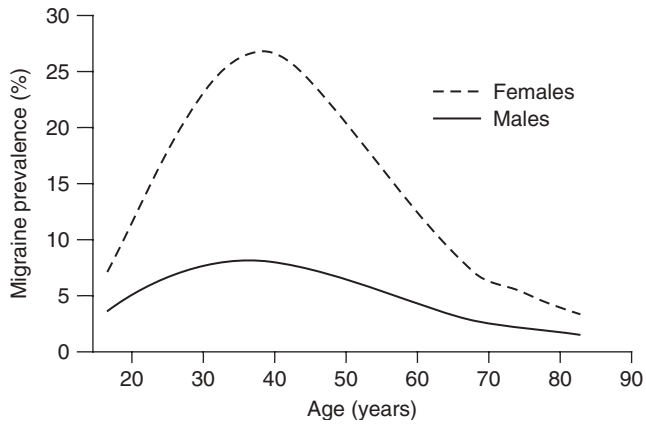

Figure 55.1 Migraine prevalence by age. Prevalence increased from 12 to 38 years of age in both women and men; the peak was considerably higher among women. Reprinted from S.D. Silberstein and R.B. Lipton, Headache epidemiology: emphasis on migraine. *Neurologic Clinics*, 1996;**14**:421–34, Copyright 1996, with permission from Elsevier.

the effectiveness and adverse effects of treatment. Patients should bring their medications with them periodically to check for compliance and to see if other physicians have prescribed any additional medications.

Table 55.2 Headache in the elderly.

Less common	Equally common	More common	Typically in the elderly
Migraine	Cluster headache	Intracranial lesions	Giant cell arteritis
Tension-type headache	Cervicogenic headaches	Medication-induced (except rebound)	Hypnic headache
		'Metabolic headache'	Headache of Parkinson's disease
		Anaemia	Trigeminal neuralgia
		Hypoxia	
		Hypercalcaemia	
		Hyponatraemia	
		Chronic renal failure	
		Cerebrovascular disease	

Table 55.3 Worrisome headache flags (SNOOP).

System symptoms (fever, weight loss) or
Secondary risk factors (HIV, systemic cancer)
Neurological symptoms or abnormal signs (confusion, impaired alertness or consciousness)
Onset – sudden, abrupt or split-second
Older – new onset and progressive headache, especially in middle-age >50 years (giant cell arteritis)
Previous headache history – first headache or different (change in attack frequency, severity or clinical features)

Source: American Headache Society and American Academy of Neurology. *Neurology Ambassador Program for Continuing Medical Education*, 2001; GlaxoSmithKline Grant.

Primary headaches in the elderly

Migraine

Migraine occurs in 18% of women, 6% of men and 4% of children in the USA;[4] 62% of migraineurs also have TTH. Migraine usually begins in the first three decades of life and prevalence peaks in the fifth decade. The prognosis for migraine sufferers is good, since migraine prevalence decreases with increasing age. Although migraine can begin after age 50 years, a secondary organic cause must be considered when this occurs. In one study, only one of 193 patients with headache beginning after age 65 years had migraine. Cull[5] collected 10 patients with migraine onset after age 60 years, two of whom had strokes on computed tomography (CT) finding. The ratio of migraine with aura to migraine without aura was reversed (86%:14%) among new onset migraine patients older than age 40 years.

Whether this is due to referral patterns or biological factors is uncertain.

Migraine prevalence decreases with menopause, although the prevalence does not fall to premenarchal levels. The frequency of migraine aura without headache (migraine equivalents) in the elderly is unknown. In community-based studies, migraine prevalence varied from 0.3% in China (age >70 years) to 12% in Boston (age >65 years). In some, but not all, studies migraine prevalence continued to decrease in the very elderly.[4]

Clinical features of migraine

Migraine is an episodic headache disorder whose diagnosis depends on the characteristics of the pain and associated features. The ICHD-II criteria for migraine without aura (Table 55.4) require the patient to have at least five headache attacks.[1] With time, the associated symptoms of migraine decrease, in part accounting for the decrease in migraine prevalence, since the headaches may no longer meet ICHD-II migraine criteria. The migraine aura may occur without the headache and migraine may remit or become transformed into CM (with or without medication overuse).

A diagnosis of migraine with aura (classic migraine) requires the patient to have at least two attacks with at least three of the characteristics listed in Table 55.5. If the aura lasts longer than 1 h but less than 1 week, the condition is called *migraine with prolonged aura*.[1] Migraine is more than just an aura and a headache. Some patients have four phases: the premonitory phase, the aura, the headache and the postdrome. About 60% of patients have a prodrome, which occurs hours to days before the headache. During this time, patients may have various psychological, sensory, constitutional or autonomic symptoms. Not all patients experience a prodrome, but if they do, their prodromal symptoms are usually the same each time. The symptoms can continue into the aura and headache phases.[6] The aura develops over 5–20 min, lasts from 20 to 30 min and consists of focal neurological symptoms that accompany the headache or occur up to 1 h before it begins. About 20% of migraineurs experience an aura, which may be visual, sensory or motor or involve speech disturbances. Visual symptoms are the most common and include scintillations (fluorescent flashes of light in the visual field), fortification spectra or teichopsia (alternating light and dark lines in the visual field), photopsia (flashing lights) and positive (bright geometric lights in the visual field) and negative (blind spots that may move across the visual field) scotomata. Sensory symptoms include numbness, tingling or paraesthesias of the face or hand.

Motor symptoms are usually hemiparetic, while language disturbances consist of difficulty in speaking (aphasia) or understanding.[6] The headache can begin at any time during the day. The pain usually develops gradually and then subsides after 4–72 h. A headache lasting longer than 72 h defines status migrainosus. The pain is usually located in the temples, but it can occur anywhere in the face or head

Table 55.4 Migraine without aura.

Diagnostic criteria

A At least 5 attacks fulfilling criteria B–D
B Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C Headache has at least two of the following characteristics:
  1 Unilateral location
  2 Pulsating quality
  3 Moderate or severe pain intensity
  4 Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D During headache at least one of the following:
  1 Nausea and/or vomiting
  2 Photophobia and phonophobia
E Not attributed to another disorder

Table 55.5 Migraine with aura.

Diagnostic criteria

A At least 2 attacks fulfilling criterion B
B Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1–1.2.6
C Not attributed to another disorder

1.2.1 Typical aura with migraine headache

Diagnostic criteria

A At least 2 attacks fulfilling criteria B–D
B Aura consisting of at least one of the following, but no motor weakness
  1 Fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)
  2 Fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
  3 Fully reversible dysphasic speech disturbance
C At least two of the following:
  1 Homonymous visual symptoms and/or unilateral sensory symptoms
  2 At least one aura symptom develops gradually over ≥ 5 min and/or different aura symptoms occur in succession over ≥ 5 min
  3 Each symptom lasts ≥ 5 and ≤ 60 min
D Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 min
E Not attributed to another disorder

and may radiate down the neck and shoulder. The pain is moderate to severe in intensity and usually described as throbbing or pulsating. Pain is usually unilateral, but may begin as or become bilateral. Strictly unilateral headaches are not of concern since they occur in 20% of migraineurs. Accompanying symptoms are common: most patients are anorectic and have nausea; some vomit or have diarrhoea. Photophobia and phonophobia cause patients to seek relief in a dark, quiet room to decrease sensory stimulation. Most patients have 1–4 attacks per month. After the headache phase, some patients experience a postdrome or recovery phase that may last up to 24 h. Some patients feel tired, others feel alert, some feel depressed, others feel euphoric, some feel worn out, and some feel refreshed. Some may complain of poor concentration, food intolerance or scalp tenderness. Medications that are more commonly used by the elderly may exacerbate or trigger migraine. Analgesic, ergotamine or triptan overuse can cause CDH in patients of all ages. Nitroglycerine and other nitrates may exacerbate migraine. Estrogen replacement therapy may either exacerbate or ameliorate migraine. Reserpine, an antihypertensive agent, is a recognized migraine trigger.

Migraine equivalents of the elderly

In the elderly, migraine aura without headache (acephalic migraine) is also called *late-life migraine accompaniments*. It may occur for the first time in a patient over the age of 40 years.[7] Its diagnosis is particularly treacherous in patients with no prior history of migraine and should be made by exclusion unless the symptoms are pathognomonic of the migraine aura (e.g. scintillating scotomata lasting 30 min). Features are listed in Table 55.6. The headaches are usually absent or mild, if present at all, and neuroimaging is normal. The IHS diagnostic criteria are the same as in Table 55.5, migraine with aura, except for no headache.[1] Cerebrovascular disease (cerebral embolism or thrombosis, carotid or vertebral dissection, subclavian steal syndrome), epilepsy, polycythaemia, lupus anticoagulant, hyperviscosity syndrome and psychiatric spells must always be considered in the differential diagnosis and must be ruled out by the appropriate studies.[2] A syndrome of recurrent somatosensory aura, sometimes followed by a headache and associated with small cortical subarachnoid haemorrhage, has recently been described; 3–7 episodes occurred over 2 days to 5 months.[8]

Table 55.6 Migraine equivalents.

1	Gradual appearance of focal neurological symptoms' spread or intensification over a period of minutes
2	Positive visual symptoms characteristic of 'classic' migraine, specifically fortification spectra (scintillating scotoma), flashing lights, dazzles
3	Previous similar symptoms associated with a more severe headache
4	Serial progression from one accompaniment to another
5	The occurrence of two or more identical spells
6	A duration of 15–25 min
7	Occurrence of a 'flurry' of accompaniments
8	A generally benign course without permanent sequelae

Table 55.7 Migraine treatment.

Acute (symptomatic)	
	Specific – for migraine only
	Non-specific – for any pain disorder or associated symptoms
Preventive (prophylactic)	
	Pre-emptive – immediately prior to triggering event
	Short-term – for a limited time
	Chronic – continuous

Treatment of migraine headache in the elderly

Headache treatment begins with making the diagnosis and explaining it to the patient, since all treatment depends on establishing a therapeutic relationship. Drug treatment may be acute, preventive or both, supplemented by nonpharmacological treatment (Table 55.7). Acute migraine treatments are listed in Table 55.8. Because of an increased risk of cardiovascular disease, ergot alkaloids, triptans and other vasoconstrictors, such as isometheptane mucate (present in Midrin), must be used with caution, if at all, in the elderly. Benzodiazepines and barbiturates may cause excessive sedation; the long-acting benzodiazepines, in particular, may cause excessive side effects due to slowed metabolic clearance. Antiemetic drugs and neuroleptics are more likely to cause tardive dyskinesia in the elderly. Even nonsteroidal anti-inflammatory drugs (NSAIDs) may cause cognitive side effects and are associated with an increased risk of gastrointestinal bleeding [9].

Preventive treatments (Table 55.9) may also cause more side effects and be less well tolerated in the elderly. Therefore, they should be started at a very low dose and increased slowly. The tertiary amine tricyclic antidepressant agents, such as amitriptyline and doxepin, which are potent anticholinergic agents, should be used with caution. They can exacerbate glaucoma, produce visual blurring and cause problems with cognition. Nortriptyline, a secondary amine, is a reasonable alternative and generally has less pronounced side effects. The selective serotonin reuptake inhibitors, although not as effective, are very safe in the elderly. Antihypertensive drugs may cause more hypotension or lethargy in the elderly than in younger patients. Divalproex sodium and topiramate have a particularly good benefit-to-side effect profile in the elderly.

Table 55.8 Acute medications: efficacy, side effects, relative contraindications and indications[a].

Drug	Efficacy[b]	Side effects[b]	Comorbid	
			Relative contraindications	Relative indication
Acetaminophen	1+	1+	Liver disease	Pregnancy
Aspirin	1+	1+	Kidney disease, ulcer disease, PUD, gastritis (age <15 years)	CAD, TIA
Butalbital, caffeine and analgesics	2+	2+	Use of other sedative; history of medication overuse	
Caffeine adjuvant	2+	1+	Sensitivity to caffeine	
Isometheptene	2+	1+	Uncontrolled HTN, CAD, PVD	
Opioids	3+	3+	Drug or substance abuse	Pregnancy; rescue medication
NSAIDs	2+	1+	Kidney disease, PUD, gastritis	
Dihydroergotamine			CAD, PVD, uncontrolled HTN	Orthostatic hypotension, prominent nausea or vomiting
Injections	4+	2+		
Intranasal	3+	1+		
Ergotamine			Prominent nausea or vomiting, CAD, PVD, uncontrolled HTN	
Tablets	2+	2+		
Suppositories	3+	3+		
Triptans			CAD, PVD, uncontrolled HTN	
Almotriptan				
Tablets	3+	1+		
Eletriptan		1+		
Tablets	3+	1+		
Frovatriptan		1+		
Tablets	2+	1+		
Naratriptan		1+		
Tablets	2+	1+		
Rizatriptan				
Tablets	3+	1+		
Sumatriptan				
s.c. injection	4+	1+		Prominent nausea or vomiting
Intranasal	3+	1+		
Tablets	3+			
Zolmitriptan				
Intranasal	3+	1+		Prominent nausea or vomiting
Tablets	3+	1+		

[a]PUD, peptic ulcer disease; PVD, peripheral vascular disease; CAD, coronary artery disease; TIA, transient ischaemic attack; HTN, hypertension; NSAIDs, non-steroidal anti-inflammatory drugs; s.c., subcutaneous.
[b]Ratings are on a scale from 1+ (lowest) to 4+ (highest) based on response rates and consistency of response in double-blind placebo-controlled trials and our clinical experience.

Methysergide (no longer available in the USA) and methylergonovine are relatively contraindicated because they are vasoconstrictors and may cause cardiac ischaemia.[9]

Non-pharmacological treatment in the elderly, as in all patients, is attractive because it avoids medications that may present risks or cause excessive side effects. Elimination of triggers, proper diet, regular sleep and avoidance of excess caffeine and overuse of over-the-counter medications are useful modalities for all patients. Biofeedback may not be as effective in the elderly patient. The most important non-pharmacological approach involves the meticulous identification and treatment of comorbid medical and psychiatric conditions. Cervical triggers and other sources of pain should be treated with physical modalities if possible. Depression is extremely common and should be addressed.[9]

Tension-type headache (TTH)

TTH is the most common headache type, with a lifetime prevalence of 69% in men and 88% in women.[4] TTH can begin at any age, but onset during adolescence or young

Table 55.9 Prevention.

Drug	Efficacy[a]	Side effects[a]
Beta-blockers	4+	2+
Neurotoxins		
Onabotulinumtoxin A (CM)	3+	1+
Calcium channel blockers		
Verapamil	2+	1+
Antidepressants		
Tricyclics	4+	2+
Selective serotonin/norepinephrine reuptake inhibitors	2+	1+
Anticonvulsants		
Divalproex	4+	3+
Gabapentin	2+	2+
Topiramate	4+	2+
Non-steroidal anti-inflammatory drugs		
Naproxen	2+	2+

[a]Ratings are on a scale from 1+ (lowest) to 4+ (highest).

Table 55.10 Tension-type headache (IHS classification).

2.2 Frequent episodic tension-type headache

Diagnostic criteria

A At least 10 episodes occurring on ≥1 but <15 days per month for at least 3 months (≥12 and <180 days per year) and fulfilling criteria B–D
B Headache lasting from 30 min to 7 days
C Headache has at least two of the following characteristics:
  1 Bilateral location
  2 Pressing/tightening (non-pulsating) quality
  3 Mild or moderate intensity
  4 Not aggravated by routine physical activity such as walking or climbing stairs
D Both of the following:
  1 No nausea or vomiting (anorexia may occur)
  2 Photophobia and phonophobia are absent or one but not the other is present
E Not attributed to another disorder

2.3 Chronic tension-type headache

Diagnostic criteria

A Headache occurring on ≥15 days per month on average for >3 months (≥180 days per year) and fulfilling criteria B–D
B Headache lasts for hours or may be continuous
C Headache has at least two of the following characteristics:
  1 Bilateral location
  2 Pressing/tightening (non-pulsating) quality
  3 Mild or moderate intensity
  4 Not aggravated by routine physical activity such as walking or climbing stairs
D Both of the following:
  1 No nausea or vomiting (anorexia may occur)
  2 Photophobia and phonophobia are absent or one but not the other is present
E Not attributed to another disorder

adulthood is most common. Headache prevalence declines with increasing age; severity decreases in the women who continue to report headaches but does not change in men. Approximately 10% of patients acquire TTH after age 50 years. The IHS criteria for TTH are listed in Table 55.10. The headache may be shorter or longer in duration than migraine. TTH is mild or moderate in intensity and has no accompanying autonomic symptoms. The cause of this common disorder is unknown, but it is not related to muscular tension (patients with migraine have more muscle tension than patients with TTH).

Treatment of TTH in the elderly

Acute TTH often responds to non-pharmacological treatment. If the headache does not respond to this approach and medication is needed, many patients self-medicate with over-the-counter analgesics (aspirin, acetaminophen, ibuprofen, naproxen), with or without caffeine. Combination analgesics contain sedatives or caffeine and their use should be limited, as overuse may cause dependence. Narcotic analgesics and benzodiazepines should be avoided owing to their abuse potential. Overusing acute medications, including butalbital and analgesics, can cause ETTH to convert to CTTH.[9] Preventive therapy should be administered when a patient has frequent headaches that produce disability or may lead to acute medication overuse. Antidepressants, the medication of choice, should be started at a low dose and increased slowly every 3–7 days.

Chronic daily headache

CDH may be due to CTTH, CM, HC or NDPH and is often associated with acute medication overuse (Table 55.11). It is important to determine the subtype of CDH so that the appropriate treatment can be chosen. When concurrent depression and medication dependence accompany CDH, treatment is difficult and detoxification may be required. Refractory medication overuse headaches (MOHs) may occur when analgesics or triptans are taken more frequently than three days per week or opioids or ergotamine tartrate more often than two days per week. To avoid this situation, all acute medications must be used within defined limits.[4]

Patients overusing acute medications must be detoxified. This can be done as an outpatient by slowly tapering the offending medication if their use is not excessive, there are no risk factors and the patient can tolerate it. If the patient cannot tolerate the taper, NSAIDs or a short course (about 2 weeks) of corticosteroids may be useful. Clonidine (0.1–0.3 mg b.i.d.–t.i.d.) is helpful for treating the symptoms of opioid withdrawal and phenobarbital helps with withdrawal from short-acting barbiturates. Refractory patients often require hospitalization. Repetitive intravenous (i.v.)

Table 55.11 Chronic daily headache.

Primary
Headache duration >4 h
Transformed migraine (TM)
Chronic tension-type headache (CTTH)
New daily persistent headache (NDPH)
Hemicrania continua (HC)
Headache duration <4 h
Cluster headache
Chronic paroxysmal hemicrania
Hypnic headache
Idiopathic stabbing headache
Secondary
Post-traumatic headache (PTH)
Cervical spine disorders
Headache associated with vascular disorders [arteriovenous malformation, arteritis (including giant cell arteritis), dissection, subdural haematoma]
Headache associated with nonvascular intracranial disorders [intracranial hypertension, infection (EBV, HIV), neoplasm]
Other (temporomandibular joint disorder; sinus infection)

Table 55.12 Cluster headache.

3.1 Cluster

Diagnostic criteria

A At least 5 attacks fulfilling criteria B–D

B Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min if untreated

C Headache is accompanied by at least one of the following:
- 1 Ipsilateral conjunctival injection and/or lacrimation
- 2 Ipsilateral nasal congestion and/or rhinorrhoea
- 3 Ipsilateral eyelid oedema
- 4 Ipsilateral forehead and facial sweating
- 5 Ipsilateral miosis and/or ptosis
- 6 A sense of restlessness or agitation

D Attacks have a frequency from one every other day to 8 per day

E Not attributed to another disorder

3.1.1 Episodic cluster

Diagnostic criteria

A Attacks fulfilling criteria A–E for 3.1 *Cluster headache*

B At least two cluster periods lasting 7–365 days and separated by pain-free remission periods of ≥ 1 month

3.1.2 Chronic cluster

Diagnostic criteria

A Attacks fulfilling criteria A–E for 3.1 *Cluster headache*

B Attacks recur over >1 year without remission periods or with remission periods lasting <1 month

DHE should be used with caution because of the potential for cardiac ischaemia. High-dose i.v. corticosteroids and neuroleptics can be used instead.[4]

Cluster headache

Cluster headache prevalence is much lower than that of migraine or TTH, with a rate of 0.01–0.24% in various populations. Prevalence is higher in men (70–90%) than in women and in Caucasians than African-Americans. The most common form of cluster headache is episodic (only about 10% of cluster patients have chronic cluster headache) (Table 55.12). Cluster headache can begin at any age: it most commonly begins in the late 20s, rarely in childhood and occasionally (10%) in patients in their 60s. The prognosis of cluster headaches is guarded; it is a chronic headache disorder that may last for the patient's entire life [10].

Episodic cluster has bouts lasting 1 week to 1 year with remission periods lasting at least 1 month, whereas chronic cluster has no remission periods or remissions that last less than 1 month. Untreated, the attacks generally last from 30 to 90 min, but they may also last up to 180 min. Most patients have one or two cluster periods per year that last 2–3 months, with 1–2 attacks per day. Episodic cluster can evolve into chronic cluster. Cluster attacks may begin with slight discomfort that rapidly increases (within 15 min) to excruciating pain. Patients may say 'It's like driving a hot poker into my eye'. The attacks often occur at the same time each day and frequently awaken patients from sleep. Lacrimation, the most common associated symptom, is reported by about 83% of patients. Patients with cluster headaches should avoid alcohol and nitroglycerine. Most cluster headache patients require preventive treatment because each attack is too short in duration and too severe in intensity to treat with only abortive medication. In addition, ergotamine, DHE and sumatriptan are risky in the elderly, and oxygen inhalation, although safe, may just postpone, rather than abort, the attack. Preventive therapy for episodic cluster, in order of preference, includes calcium channel blockers, divalproex, topiramate, lithium, corticosteroids and melatonin. Long-term corticosteroids are not appropriate for chronic cluster.[10] Refractory cases have been treated with greater occipital nerve stimulation and even deep brain hypothalamic stimulation.

Hypnic headache

Hypnic headache (Table 55.13) is a rare, strictly nocturnal headache that occurs in older persons (mean age 63 years). The headache typically awakens the patient from sleep and can occur at the same time on one or more occasions per night. The headaches are usually throbbing and bilateral, last ~1 h and may be associated with nausea. There are usually no associated autonomic features. Lithium carbonate, at a low dose of 300–600 mg at bedtime, is an effective treatment. Other treatments include caffeine and indomethacin.[11]

Table 55.13 Hypnic headache.

4.5 Hypnic headache
Diagnostic criteria
A Dull headache fulfilling criteria B–D
B Develops only during sleep and awakens patient
C At least two of the following characteristics:
1 Occurs >15 times per month
2 Lasts ≥ 15 minutes after waking
3 First occurs after age of 50 years
D No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
E Not attributed to another disorder

Secondary headache disorders

Headache associated with cerebrovascular disease

Stroke incidence increases with age. In one study, headache was a feature of 17 of 29 (59%) infarcts. It is more common in large artery occlusive disease than cerebral embolism and less common in lacunar infarction. Headache in carotid artery occlusion is usually located around the eye of the occluded side. Headache location is unreliable to localize a stroke, especially for vertebrobasilar disease.

About 50% of headaches are severe enough to be 'troubling'; they may last from 8 to 24 h. Headache is present in 23–68% of patients with intraparenchymal haemorrhage; the highest headache frequency occurs in cerebellar and lobar haemorrhages. It is not clear how often the headache location predicts the site of the haemorrhage. The frequency of headache in transient ischaemic attacks (TIAs) varies from 6 to 44%. Headache was noted in 15 of 34 TIA patients occurring during, immediately before or after the neurological event. Migraine headaches occurred independent of the TIAs in 38% of these patients. It is possible that late-onset migraine is a marker for cerebrovascular disease.

Giant cell arteritis (see Chapter 94, Diseases of the joints)

GCA has a prevalence of 133 per 100 000 individuals over the age of 50 years, with women affected three times more often than men. Headache, the most frequent symptom, is present in 70–90% of patients. Pain can be intermittent or constant. The headache is often located over the temples and associated with scalp tenderness. Symptoms of polymyalgia rheumatica, which include muscle pain and joint stiffness, are present in 25% of patients. Other common symptoms include fever, weight loss, night sweats, masseter claudication, tongue ischaemia, amaurosis fugax (which may be bilateral in half), permanent blindness (often without warning) or partial visual loss due to anterior ischaemic optic neuropathy. Amaurosis fugax is particularly ominous; if it is not treated, about half of patients will become blind.

Induration and tenderness of the temporal or occipital scalp arteries are the most common signs of GCA. Optic disc oedema and visual loss may occur. Altitudinal defects and central scotomas breaking into the periphery are frequently seen. Diplopia is rare and, when present, is due to extraocular muscle ischaemia. True cranial nerve palsy is very uncommon. Arterial bruits or diminished pulses are present in one-third of patients. Aortic arch syndrome may occur with rupture.

The most consistent laboratory abnormality is an elevation of the erythrocyte sedimentation rate (measured by the Westergren method). Wall et al. reported that 41% of patients had a value $>100\,\text{mm h}^{-1}$ and 89% had a value $>50\,\text{mm h}^{-1}$.[12] Elevated C-reactive protein, mild liver function abnormalities and mild hyperchromic or hypochromic anaemia are common. Temporal artery biopsy, the diagnostic gold standard, should be performed within 1 week of initiating steroid treatment. Colour-coded duplex sonography helps identify the most appropriate part of the superficial temporal artery to biopsy. A long piece of artery should be obtained and multiple sections examined to improve yield. If the biopsy is negative and the index of suspicion is high, more sections should be examined and a second temporal artery biopsy done. Corticosteroids should be started as soon as possible to prevent blindness.

Headache associated with mass lesions

Headache frequently accompanies subdural haematoma: in one series it occurred in 62% of patients. Headache occurs at presentation in up to half of patients with brain tumours and develops during the course of the disease in 60%. Headache is partly dependent on tumour location: it is a rare initial symptom in patients with pituitary tumours, craniopharyngiomas or cerebellopontine angle tumours. In older, pre-CT or MRI series of brain tumour patients, headache occurred as often without as it did with elevated intracranial pressure. The headache, although usually generalized, could overlie the tumour.

Postulated mechanisms of headache development include traction on pain-sensitive intracerebral vessels, transient herniation of hippocampal gyri, traction on cranial or cervical nerves, elevation of intracranial pressure or activation of a quiescent headache disorder. Although increased cerebrospinal fluid (CSF) pressure is not necessary for headache development, it clearly plays a role in a group of patients with central nervous system neoplasms.

In a modern series, 111 consecutive patients with primary (34%) or metastatic (66%) brain tumour were

diagnosed with neuroimaging. Increased intracranial pressure was defined by the presence of papilloedema, obstructive hydrocephalus, communicating hydrocephalus from leptomeningeal metastasis or a lumbar puncture opening pressure >250 mm of CSF. Headache, present in 48% of both primary and metastatic tumours, was similar to TTH in 77% of patients and to migraine in 9%. Unlike true TTH, brain tumour headaches were worsened by bending in 32% and nausea or vomiting was present in 40%.

About 86% of patients with increased intracranial pressure had headache that was typically frontal in location and pressure-like or aching in character. Only 1% had a unilateral headache. The headache was constant in 61%. The pain was severe in intensity, associated with nausea and vomiting and resistant to common analgesics. Ataxia was present in 61%. In contrast, only 36% of patients with a supratentorial tumour without increased intracranial pressure had headache. These headaches were milder and more likely to be intermittent (however, they were constant in 20% of patients). Nausea, vomiting and ataxia were much less common.

Patients with a history of prior headache were more likely to have brain tumour headache. In many cases this headache was similar in character to the prior headache, but it was more severe or frequent or associated with neurological signs or symptoms.

In another prospective study of patients with brain tumour, only 8% had headache as their first and isolated clinical manifestation at the time of diagnosis; 31% had headache, but only one of the original patients continued to have headache as an isolated symptom.

There is a significant overlap between brain tumour headache and migraine and TTH. Any neurological sign or symptom that occurs with a headache and cannot be easily explained by the aura of migraine, a headache of recent onset or a headache that has changed in character requires a thorough evaluation, particularly if the headache is severe or is accompanied by nausea or vomiting. Increased headache frequency and morning or nocturnal headache associated with vomiting can be seen with both migraine and brain tumour. Brain tumour headache is more common in patients with a history of prior headache, increased intracranial pressure and large tumours with a midline shift.

In space-occupying lesions other than brain tumours, such as subdural haematomas and brain abscesses, headache is a more frequent and earlier symptom. McKissock[13] reported that 81% of 216 patients with chronic subdural haematoma had headache, with a lesser prevalence in acute (11%) and subacute (53%) subdural haematomas. The difference in headache prevalence between tumour and subdural haematoma is believed to be due to the more rapid evolution and greater extent of the haematomas. The lesser occurrence of headache in acute and subacute subdural haematomas compared with chronic subdural haematoma may be due to the underlying traumatic cerebral changes in the former obtunding consciousness early and making it difficult to elicit a history of headache. The headache is often ipsilateral to the subdural haematoma or brain tumour.

Patients with brain abscesses often have a progressively severe, intractable headache. In published clinical series, headache was present in 70–90% of patients. The higher headache prevalence in abscess, compared with tumour, may be due to its faster evolution, the associated meningeal reaction and the occasional low-grade fever that may accompany abscess.

Parkinson's disease (see Chapter 63, Parkinson's disease)

The association between Parkinson's disease and headache is controversial. In one series, headache occurred in 41% of patients with Parkinson's disease and 13% of controls. Another controlled series found no difference in headache prevalence. Possible headache mechanisms include comorbid depression and muscle rigidity. In one study of early-morning occipital headache in Parkinson's disease, headache failed to improve with treatment directed at muscle spasm, but did improve with levodopa.

Medication-induced and toxic headache

Medications used for the treatment of coexisting disease may trigger headaches. These include nitrates, some calcium channel blockers, estrogens and progestins, histamine receptor blockers, theophylline and NSAIDs. Overuse of caffeine, analgesics, narcotics, ergotamine and triptans can lead to CDH.

Carbon monoxide poisoning frequently presents with headache. Headache is moderate in intensity, has no characteristic location and may be accompanied by weakness, lethargy, confusion, photophobia or phonophobia. Often other members of the household have similar symptoms.[14]

Post-traumatic headache

Age is probably neither protective nor conducive to the development of post-traumatic headache after mild head injury. The features of post-traumatic headache are variable and diagnosis requires the onset of a new kind of headache (substantially different from previous headaches) within 7 days of the head injury or of regaining consciousness from the head trauma. Increasing age is associated with less rapid and less complete recovery.

Table 55.14 Cervicogenic headache.

11.2.1 Cervicogenic headache

Diagnostic criteria

A Pain, referred from a source in the neck and perceived in one or more regions of the head and/or face, fulfilling criteria C and D

B Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache

C Evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following:
  1 Demonstration of clinical signs that implicate a source of pain in the neck
  2 Abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo or other adequate controls

D Pain resolves within 3 months after successful treatment of the causative disorder or lesion

Headaches associated with disorders of the cervical spine

The association between disease of the spine and headache is controversial. The IHS has adopted restrictive criteria for these headaches. Generally accepted causes of headache related to cervical spine lesions, and also currently controversial causes, are listed in Table 55.14. Many of the non-controversial causes of cervicogenic headache (such as Paget's disease and tumours) are more common in the elderly. Radiographic spondylosis worsens with age but its relationship to headache is uncertain. If the patient has non-headache indications for MRI or EMG, such as myelopathy or radiculopathy, these disorders can be diagnosed and treated on their own merit. Tender spots can be treated with an injection of local anaesthetic and corticosteroids.

Glaucoma

Primary open-angle glaucoma, the most common cause of glaucoma, is rarely painful. Miotic eyedrops used in its treatment may produce brow ache. Acute angle closure glaucoma is less common and may produce intense eye pain that radiates widely and may be associated with nausea and sinus area pain; it is often associated with a red eye, fixed mid-pupil position, corneal cloudiness and a red sclera. Laser iridotomy is curative. Secondary angle closure glaucoma resulting from diabetes or carotid insufficiency may produce a deep, boring, unrelenting pain associated with a red eye and poor vision. To make the diagnosis of glaucoma-related headache, the pain should develop simultaneously with the glaucoma and be relieved within 72 h of effective treatment.

Sinusitis

Acute purulent sinusitis produces severe headache associated with purulent nasal discharge. A dangerous exception to this rule is sphenoid sinusitis, which may present as a severe, intractable, progressive headache.

Other head and facial pain syndromes affecting the elderly

Trigeminal neuralgia

Trigeminal neuralgia is the most common neuralgic syndrome, with a peak incidence in the sixth and seventh decades (Table 55.15). Secondary trigeminal neuralgia usually presents at a younger age. Trigeminal neuralgia is typically unilateral, but is bilateral in 4% of patients. Symptoms include repetitive jolts of electric-like pain in the distribution of one or more divisions of the trigeminal nerve. The paroxysms of pain are characteristically induced by touching a 'trigger zone' in the relevant division of the fifth cranial nerve. Brushing the teeth, chewing, talking or even a wisp of air on the face can trigger an attack. Between paroxysms, a sustained, deep, dull ache may be present.

Pretrigeminal neuralgia is a dull, continuous, achy pain in the jaw, which may be provoked by pressure about the face or mouth, and may evolve into trigeminal neuralgia. It may account for many of the cases of trigeminal neuralgia diagnosed after multiple dental procedures, since the clinical features are not distinctive.

The diagnosis of trigeminal neuralgia is established by typical clinical features and an examination that is negative except for positive trigger points; diagnostic studies are generally normal. Impaired sensation in the distribution of the fifth nerve suggests a structural, demyelinating or compressive trigeminal nerve lesion. Aneurysms, GCA, intracranial tumours, dental mandibular malignancy or cranial malignancy can produce the symptoms of trigeminal neuralgia associated with decreased facial sensation. Multiple sclerosis, dental pathology or a dental procedure can produce a

Table 55.15 Cranial neuralgias.

13.1.1 Classical trigeminal neuralgia

Diagnostic criteria

A Paroxysmal attacks of pain lasting from a fraction of a second to 2 min, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C

B Pain has at least one of the following characteristics:
  1 Intense, sharp, superficial or stabbing
  2 Precipitated from trigger areas or by trigger factors

C Attacks are stereotyped in the individual patient

D There is no clinically evident neurological deficit

E Not attributed to another disorder

pattern of pain indistinguishable from trigeminal neuralgia. The natural history of trigeminal neuralgia is variable. Periodic remissions are common, but permanent spontaneous remissions are rare. Over 50% of patients have a remission that lasts 6 months or more.

Trigeminal neuralgia is thought to be due to focal demyelination of the trigeminal nerve. In 80–90% of cases, this is caused by vascular compression from abnormal arterial loops near the root entry zone of the nerve. Aberrant neuronal activity may arise from these injured areas, which could promote changes in the trigeminal nucleus caudalis.

Medical treatment is usually successful (Figure 55.2, Table 55.16). Drugs used include gabapentin, carbamazepine, oxcarbazepine, phenytoin, baclofen, valproic acid, clonazepam and pimozide, alone or in combination. Combination therapy is often effective and necessary. Phenytoin can be given intravenously to control especially painful paroxysms.

If medication fails to control symptoms adequately, ablative procedures should be considered. Alcohol or glycerol injections may be used. More proximal injections produce better long-term results. Gasserian ganglion injections have a 5 year recurrence rate of 41–86%. Retrogasserian glycerol injections can produce mild facial numbness, but painful dysaesthesias are rare and anaesthesia dolorosa is absent. The mean recurrence time varies from 6 to 47 months. Percutaneous balloon compression of the trigeminal ganglia may be similarly effective. Radiofrequency gangliolysis provides relief in 82–100% of patients and has a recurrence rate between 9 and 28%. Major complications are rare; loss of corneal reflex occurs in as many as 70% of patients and masseteric weakness occurs in approximately half, but improves over 3–6 months. Minor paraesthesias occur in about 10%, but anaesthesia dolorosa is rare.

The Janetta procedure, performed via an occipital craniotomy, separates aberrant blood vessels, if present, from the trigeminal nerve root. Long-term benefit is reported in over 80% of patients, with recurrence rates of 1–6%. Surgical mortality is 1% and serious morbidity 7%. Because of this, other less invasive surgical procedures, such as percutaneous glycerol injection and radiofrequency rhizotomy, which have less morbidity, are often tried first, even though they may be only temporarily effective. More recently, several radiosurgical techniques aimed at the trigeminal nerve root adjacent to the pons have been successful.

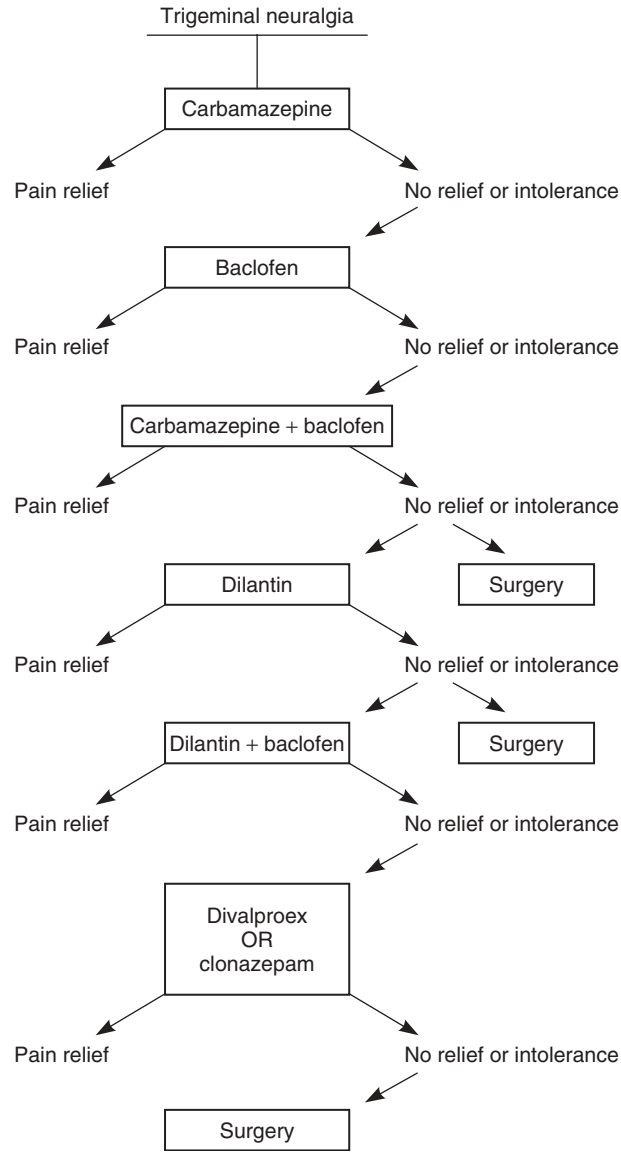

Figure 55.2 A proposed algorithm for the medical treatment of trigeminal neuralgia. Once the patient has been pain free for 3–6 months on a medication, the drug should be slowly tapered off to avoid medicating during spontaneous remission. If the pain recurs, the medication is reinstituted. Individual needs may dictate earlier surgery. Modified from J.C. Masdeu, Medical treatment and clinical pharmacology. In: R.L. Rovit, R. Murali and P.J. Jannetta (eds), *Trigeminal Neuralgia*, Williams and Wilkins, Baltimore, 1990, pp. 79–84.

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia (Table 55.17) is less common than trigeminal neuralgia. The unilateral pain occurs in the distribution of the glossopharyngeal and vagus nerves in and around the ear, jaw, throat, tongue or larynx. Radiation from the oropharynx to the ear is common. Paroxysms of jabbing or electric pain last for about 1 min and may be accompanied by deep, continuous pain between paroxysms.

Table 55.16 Characteristics of antineuralgic drugs.

Drug	Bioavailability (%)	Time to maximum concentration (h)	Half-life (h)	Time to steady-state concentration (days)	Therapeutic 'target' range^{-1}) (μmol l^{-1})
Baclofen	–	3–8	3–4	1	–
Carbamazepine	>70	2–8	11–27	5	24–43
Clonazepam	100	1–2	24–48	12	30–270
Lamotrigine	100	2–3	18–30	8	4–16
Oxcarbazepine	100	1–2	14–26	7	35–110
Phenytoin	98	4–8	15–20	14	20–80
Valproic acid	99	1–4	6–17	5	200–700

Modified from J.M. Zakrzewska, Trigeminal neuralgia. In: J.M. Zakrzewska (ed.), *Major Problems in Neurology*, W.B. Saunders, Philadelphia, PA, 1995, pp. 108–70.

Table 55.17 Glossopharyngeal neuralgia.

13.2.1 Classical glossopharyngeal neuralgia

Diagnostic criteria

A Paroxysmal attacks of facial pain lasting from a fraction of a second to 2 min and fulfilling criteria B and C

B Pain has all of the following characteristics:
  1 Unilateral location
  2 Distribution within the posterior part of the tongue, tonsillar fossa, pharynx or beneath the angle of the lower jaw and/or in the ear
  3 Sharp, stabbing and severe
  4 Precipitated by swallowing, chewing, talking, coughing and/or yawning

C Attacks are stereotyped in the individual patient

D There is no clinically evident neurological deficit

E Not attributed to another disorder

Patients may have as many as 30–40 attacks per day and may be awakened from sleep. Paroxysms of pain may be triggered by chewing, talking, yawning, coughing or swallowing cold liquids. Stimulation of the external auditory canal and postauricular area may also provoke pain. In ~2% of cases, syncope (secondary to bradycardia or asystole) and seizures (from cerebral ischaemia) have occurred. Atropine prevents syncope, which suggests that vagal afferent discharge is its mechanism.

The diagnosis of glossopharyngeal neuralgia is clinical. Neurological examination is usually normal. Other disorders are ruled out by history, physical examination and diagnostic testing. The assumed cause of glossopharyngeal neuralgia is nerve compression from aberrant blood vessels. Symptomatic causes of a glossopharyngeal neuralgia-like syndrome include cerebellopontine angle tumour, nasopharyngeal carcinoma, carotid aneurysm, peritonsillar abscess and compression from an osteophytic stylohyoid ligament lateral to the glossopharyngeal nerve.

Table 55.18 Chronic postherpetic neuralgia.

13.15.2 Postherpetic neuralgia

Diagnostic criteria

A Head or facial pain in the distribution of a nerve or nerve division

B Herpetic eruption in the territory of the same nerve

C Pain preceded herpetic eruption by <7 days

D Pain persists after 3 months

The best diagnostic test involves anaesthetizing the tonsil and pharynx, which can temporarily terminate a painful paroxysm and confirm the diagnosis. Drug treatment is the same as for trigeminal neuralgia. Surgical treatment involves intracranial sectioning of the glossopharyngeal nerve and the upper rootlets of the vagus at the jugular foramen. A microvascular decompression procedure has been described.[15]

Postherpetic neuralgia

Postherpetic neuralgia (Table 55.18) follows an attack of acute herpes zoster, evolving as the acute attack subsides. One definition is the presence of pain more than 1 month after the eruption of zoster. Old age, diabetes mellitus, ophthalmic herpes zoster and a compromised immunological system increase the risk for postherpetic neuralgia. Postherpetic neuralgia is a significant cause of head pain in the elderly.

Acute zoster often begins with paraesthesias and pain in the affected region, followed 4–5 days later by a vesicular eruption. Most patients have a deep aching or burning pain, paraesthesias and dysaesthesias. Some may have hyperaesthesia or electric shock-like pains. Typical involvement in the head occurs unilaterally in the distribution of the ophthalmic or maxillary divisions of the trigeminal nerve or at the occipitocervical junction. Ophthalmic herpes may be associated with diplopia due to involvement of cranial nerves III, IV and VI. Geniculate herpes is associated with

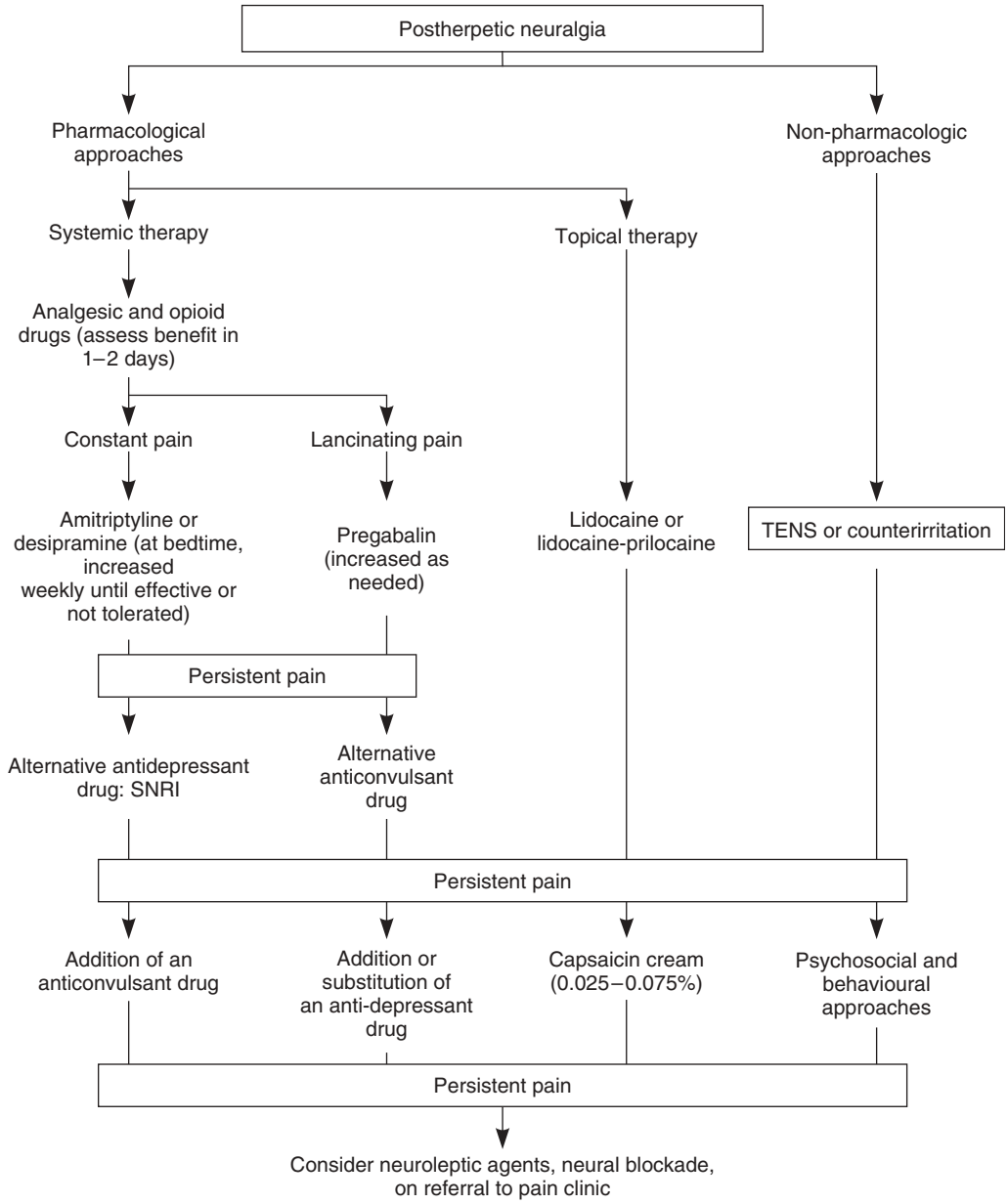

Figure 55.3 Algorithm for the treatment of persistent postherpetic pain. Modified from Kost and Straus.[16]

facial palsy (CN VII). Vesicles are often seen in the external auditory canal.

The incidence of postherpetic neuralgia depends on its definition, which varies from pain persisting for 1 month to pain persisting for 6 months. Age, severity and the presence of uraemia correlate with developing postherpetic neuralgia. It is more common in the elderly, occurring in 5% of patients with acute zoster who are below 40 years of age, in 50% of those in the seventh decade and in 75% of those above 70 years of age. Slow, spontaneous improvement of pain occurs in most patients; in 3 years, 56% of patients are either completely pain free or have non-troublesome pain.

The pain occurs in areas overlying abnormal hyperaesthetic skin and has three components: (1) constant, deep, burning pain; (2) repetitive stabs and needle pricking sensations; and (3) superficial, sharp, radiating or itch sensation provoked by light touch. Sleep is often interrupted. Postherpetic neuralgia may reflect a deafferentation pain syndrome and may be accompanied by increased sympathetic activity.

Topical therapies such as compresses of Burow's solution, colloidal oatmeal or calamine lotion are used to treat acute zoster. The skin should be protected with sterile dressings. Oral glucocorticoids may lead to faster resolution of acute zoster pain, but it is not clear if they have

any value in preventing or attenuating postherpetic neuralgia. Antiviral agents may attenuate acute herpes zoster in immunocompromised patients. Acyclovir used for 21 days may ameliorate pain in the acute phase. Famciclovir, valacyclovir and brivudin may be superior to acyclovir. Acyclovir and famciclovir have not been proven to reduce the risk of postherpetic neuralgia. Epidural blockade or sympathetic blockade may help pain acutely and may reduce postherpetic neuralgia.

Postherpetic neuralgia should be treated as soon as the diagnosis is made. Amitriptyline is commonly used, but nortriptyline or desipramine may be preferable, since they have fewer anticholinergic side effects. Gabapentin and pregabalin were studied in several double-blind, placebo-controlled trials to control pain (at doses of gabapentin from 2400 to 3600 mg per day or pregabalin at 600 mg per day). Capsaicin, a substance-P depleter, may be of some benefit, but burning may limit its usefulness. Topical NSAIDs may be useful. Local anaesthetic preparations are also effective. Peripheral and central surgical techniques are of little, if any, value (Figure 55.3)[16].

Key points

- The International Headache Society (IHS) divides headaches into two broad categories: primary and secondary headache disorders.
- With ageing, not only is there a change in prevalence of the primary headache disorder but also a shift to new or organic causes of headache.
- Headache is common in the elderly.
- The evaluation of the elderly patient with headache must be directed to rule out serious secondary causes of headache such as tumour, subdural haematoma, stroke, transient ischaemic attack and temporal arteritis.
- Medications that are more commonly used by the elderly may exacerbate or trigger migraine.
- In the elderly, migraine aura without headache (acephalic migraine) is also called late-life migraine accompaniments.
- Hypnic headache is a rare, strictly nocturnal headache that occurs in older persons.
- Giant cell arteritis occurs in 3–9 per 100 000 patients over the age of 50 years, with women affected three times more often than men.
- The association between Parkinson's disease and headache is controversial.
- Trigeminal neuralgia is the most common neuralgic syndrome in the elderly, with a peak incidence in the sixth and seventh decades.

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CHAPTER 56

Normal pressure hydrocephalus

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Introduction

Normal pressure hydrocephalus (NPH) is a condition that is characterized by the clinical triad of gait disturbance, cognitive decline and urinary incontinence. It is further supported by imaging evidence of ventriculomegaly. The typical age group involved is above 60 years, although it can occur as early as 50 years,. Because it generally occurs in the geriatric population, detection may be challenging as the symptoms overlap with those of other degenerative neurological conditions and sometimes the decline may even be attributed simply to old age. It is therefore important that NPH be kept in mind when evaluating relevant patients. Its incidence has been estimated at 1.8 cases per 100 000,[1] but others have it higher at 5.5 per 100 000.[2] One study even estimated that the prevalence may be 14% in assisted-living facilities.[3] Regardless of the numbers, many feel that it is an under-recognized condition so there has been a push to highlight its importance not just among healthcare providers but also the general population so that family members may bring potential patients to medical attention.

NPH is widely accepted to have been first identified in 1965,[4] but it was recognized as early as 1957 by Dr. Salomon Hakim, who is regarded as the father of NPH.[5] The name was derived from his observation that such patients did not present with papilloedema and had normal cerebrospinal fluid (CSF) pressures on lumbar puncture. It was a revolutionary discovery as it gave new hope that a degenerative neurological condition could now be reversed through simple CSF diversion. It should be noted that although the term 'normal pressure hydrocephalus' is widely used, changing concepts have given rise to questions on the validity of this nomenclature. Some authors have suggested, for example, that CSF pressure in NPH is not exactly 'normal' as some show abnormalities in CSF dynamics.[6] Terms such as 'chronic hydrocephalus' have been proposed, but thus far none have been convincing enough to cause a shift away from the widely used term 'NPH'.[7]

Aetiology and pathophysiology

Hydrocephalus by definition is an excessive accumulation of CSF in the ventricular system. What leads to this condition can be a host of causes ranging from haemorrhage to neoplasm. However, its aetiology can be roughly divided into two categories: non-communicating, wherein there is a blockage in the ventricular system (e.g. aqueductal stenosis); and communicating, which can result either from a decrease in CSF resorption (scarring after subarachnoid haemorrhage) or from CSF overproduction (e.g. choroid plexus papilloma). In the realm of geriatrics, it is virtually never a consequence of CSF overproduction. As far as NPH is concerned, it is commonly accepted that fluid build-up is due to impairment of the brain's CSF resorptive capacity – an idea that is known as the bulk flow theory. This can occur at the level of the arachnoid granulations along the skull base and over the hemispheres.[8] Some authors feel that resorption also occurs in the brain parenchyma through capillaries and venules[9,10] and resorptive problems can also be at this level. Among the known causes of NPH are subarachnoid haemorrhage, trauma and meningitis, all of which can lead to scarring of the arachnoid granulations in the subarachnoid space. Such conditions are commonly referred to as secondary NPH.

In over half of NPH patients, however, there is no identifiable cause. The development of idiopathic NPH remains unclear, but it appears to involve the interplay of several factors such as cerebral ischaemia, decreased vascular compliance, decreased cerebral blood flow to periventricular regions and brain atrophy. MR flow quantification studies showed lower venous compliance in NPH patients, which could lead to increased resistance to CSF outflow and cerebral ischaemia in the concerned areas.[11] Indeed, it has been shown that after shunting, cortical vein compliance is improved in patients who respond to the procedure.[12] The bulk flow theory is easily understandable but others feel that it is an oversimplification. It appears inadequate in

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explaining certain characteristics such as why CSF pressure can remain normal and why some patients improve with endoscopic third ventriculostomy (ETV), which does not involve diverting fluid volume away from the intracranial space. An alternative theory known as the hydrodynamic concept of hydrocephalus has been gaining traction. It holds that a decrease in intracranial compliance allows an increased transmission of systolic pressure to the brain parenchyma, which in turn becomes distended against the unforgiving skull.[13] Creating a hole on the floor of the third ventricle (ETV) thus allows for 'venting' of the increased systolic pressure and CSF to the subarachnoid space. The thought is that the aqueduct of Sylvius is too narrow and inadequate for venting.

There are other factors that influence the pathophysiology of NPH. Cerebral blood flow has been shown to be decreased in patients with idiopathic NPH, particularly in periventricular regions[14] and also the basal ganglia and thalamus.[15] Idiopathic NPH patients have also been found to have brain atrophy in addition to hydrocephalic features.[16] More recently, there has been an increasing awareness of the role that metabolic disturbances play in the genesis of NPH symptoms. For instance, accumulation of beta-amyloid and disturbance in cholinergic neurotransmission may contribute to cognitive and memory decline.[17] This would explain why cognitive function sometimes does not improve after shunting. It is also suggested that deterioration of striatal GABAergic neurons and lower dopamine levels in the substantia nigra could lead to motor dysfunction. This idea would account for the observation that patients who initially show gait improvement after shunting later regress despite proof that the shunt is working or even after valve pressure adjustments. Although we do not fully understand the interplay of the multiple factors that affect NPH patients, it is clear that NPH symptoms do not simply evolve from problems in CSF dynamics.

Clinical presentation

Although NPH has traditionally been associated with neurosurgeons because of its ultimate treatment, the evaluation and workup that lead to surgery require the involvement of many other medical professionals. It may be the primary care provider who casts the first suspicion or the geriatric specialist who pushes for further workup. Then there is the neuropsychologist who delineates the condition by performing neurocognitive evaluations. However, it can be argued that it is the neurologist who holds the central position as he or she has the deepest knowledge of other similar conditions that allow for better differentiation and diagnosis of NPH.[18]

It is easy to say that NPH presents with the classic triad of gait disturbance, urinary incontinence and mental decline. However, it can be challenging to assess the character of each of these symptoms since there are other conditions that may produce NPH's components. For instance, gait disturbance can be seen in movement disorders and a common differential is Parkinson's disease. Memory or cognitive decline can be seen in Alzheimer's disease; in fact, it is the more common consideration. As for bladder incontinence, there are a host of urological and neurological reasons that can be suspected. Having said all that, there are typical characteristics that we can look for when evaluating a patient who presents with these symptoms.

The most prominent symptom is usually the progressive difficulty in ambulation. It is typically described as a wide-based gait that is slow and unsteady. The patient usually walks in small steps and has poor floor clearance, that is, they do this with their feet clearing the floor at a low height. Others describe it as a feeling that the feet are glued to the floor, commonly referred to as 'magnetic feet'. The degree of gait disturbance depends on the severity of the NPH and patients who are in the early stages of the disease can walk almost normally except for some unsteadiness. It is not uncommon to encounter patients who are still highly functional and simply report a gait disturbance on walking a certain distance or against an incline. Conversely, patients with severe NPH can be so debilitated that they are unable to stand without support. Despite the advanced and severe state, their response to shunting can be very dramatic so they are not to be dismissed or given up on.

Mental decline is usually in the form of problems with memory, particularly short-term memory. It may also involve a decrease in mental alertness and an overall slowing of thought processes. The process may be so gradual that nobody notices it or it is attributed to ageing. It is important to ask family members aside from the patient because it may not be apparent to the patient himself or herself. The physician may also find it difficult to detect during the finite visit, whereas family members are able to share their observations of the patient over a longer period of time and across varying situations. Family members are crucial to the history-taking in this sense.

Urinary incontinence may start as progressive urgency, but many will have frank incontinence by the time of consultation. It is a symptom that the examiner needs specifically to ask about because it may not be recognized by the elderly patient or family members as significant. They may not realize that it is related to the overall neurological condition or the patient may be somewhat embarrassed to say that he or she is already on adult diapers. Of the clinical triad of symptoms, urinary incontinence is usually the last to develop. It is considered to be a symptom of late-stage NPH.[19]

Differential diagnosis

When dealing with the geriatric population, it is not hard to imagine that NPH symptomatology in an elderly patient

can be easily mistaken for, and brushed aside as, part of the ageing process. Awareness of this condition is not as prevalent as it should be and many patients do not come to medical attention. Indeed, one can only wonder how many patients have gone undiagnosed and have potentially missed out on a better quality of life had they been shunted.

Another challenge to identifying NPH is related to its differential diagnoses. These include Parkinson's disease, Alzheimer's disease, vascular dementia and spinal stenosis. Most commonly, it can be difficult to differentiate from Parkinson's and Alzheimer's disease. Gait similarities in NPH and Parkinson's disease include short steps and leg rigidity.[20] The typical tremor of Parkinson's disease may help make this diagnosis, but sometimes patients with NPH can also have confusing tremors. In general, it is possible to differentiate between the two by the gait patterns. NPH is characterized by reduced stride length, reduced step height and balance difficulty. Parkinson's disease patients have a shuffling gait with impaired arm swing and walk with their hips and knees slightly flexed and trunk bent forward.[21] In comparing Alzheimer's disease and NPH, the dementia is not as pronounced as in Alzheimer's disease. However, it is not uncommon to find NPH patients with concurrent Alzheimer's disease.[22] It is important to identify patients with both Alzheimer's disease and NPH, because this particular subset tends to respond poorly to shunting.[23] Given these challenges in differential diagnosis, we again emphasize the crucial role that neurologists and neuropsychologists play in the evaluation of potential NPH patients.

Diagnostic modalities

Numerous tests have been developed over the years to help in the diagnosis of NPH. Some have stuck and become incorporated into regular practice whereas others have passed on to the realm of historical interest. It is fascinating to see how the evolution of these tests reflects the dynamic ideas that have been elucidated with regard to its pathophysiology over the past five decades. As in many medical conditions, diagnostic tests are not meant to replace good history taking and physical examination. In fact, clinical acumen and computed tomography/magnetic resonance imaging (CT/MRI) play a primary role in clinching the diagnosis. However, it is important to note that the diagnostic workup for NPH is as much about diagnosis as it is about determining whether a patient will respond well to surgery. For this reason, a number of other diagnostic modalities have been developed to predict shunt responsiveness. There is still significant variability in practice as far as usage is concerned, depending on ideological and logistical differences from place to place.

CT/MRI

Imaging via CT or MRI remains the main diagnostic tool in NPH. The finding that is demonstrated is ventriculomegaly (Figure 56.1). Whereas a head CT is able to show enlarged ventricles, MRI gives additional information that may contribute to the evaluation of a patient. For instance, white matter changes in the subcortical and periventricular areas have been associated with NPH. These abnormalities appear on MRI as T2 hyperintensities (Figure 56.2). An MRI can also show flattened gyri and effaced sulci that indicate tightness in the intracranial compartment. It is important to remember, however,, that even if the arachnoid space looks 'spacious', it does not necessarily rule out the condition. MRI may also provide details that may be helpful in excluding other disease entities. For these reasons, it is probably better to order an MRI whenever feasible and it is unnecessary first to go through a CT scan. However, in places where MRI is not readily available, CT scanning is adequate for the purpose of demonstrating ventriculomegaly. It is also easier and cheaper to use CT in the postoperative period when checking for shunt position or monitoring for formation of subdural collections after shunt valve reprogramming (see below).

In the elderly population, it is common to find cerebral atrophy. This age-related thinning of the cerebral mantle is accompanied by a reciprocal dilatation of the CSF spaces including the ventricles, a finding that is commonly referred to as '*ex vacuo* dilatation'. Whether it is a CT or an MRI of

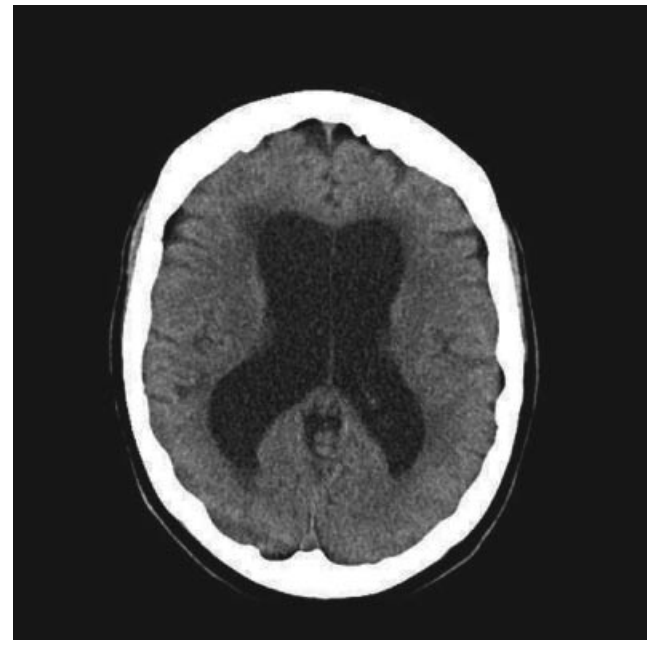


Figure 56.1 CT scan showing typical features of NPH, with ventricular enlargement out of proportion to cerebral atrophy.

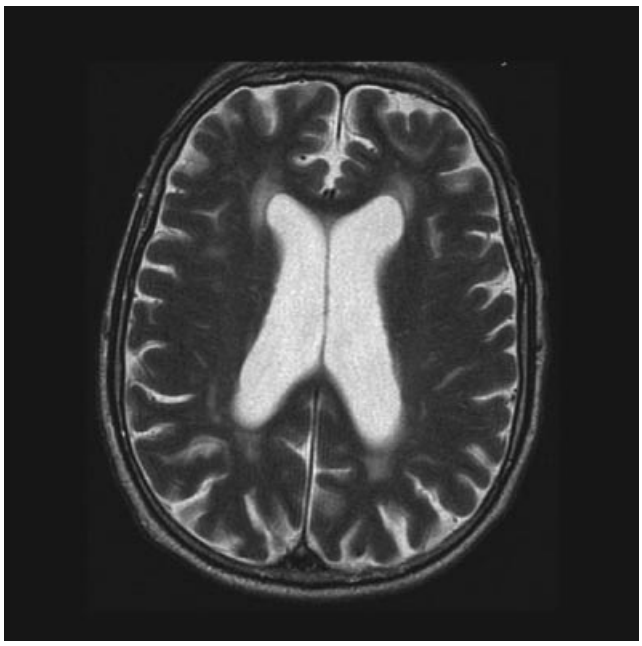


Figure 56.2 T2 sequence MRI showing white matter changes that may be seen in NPH.

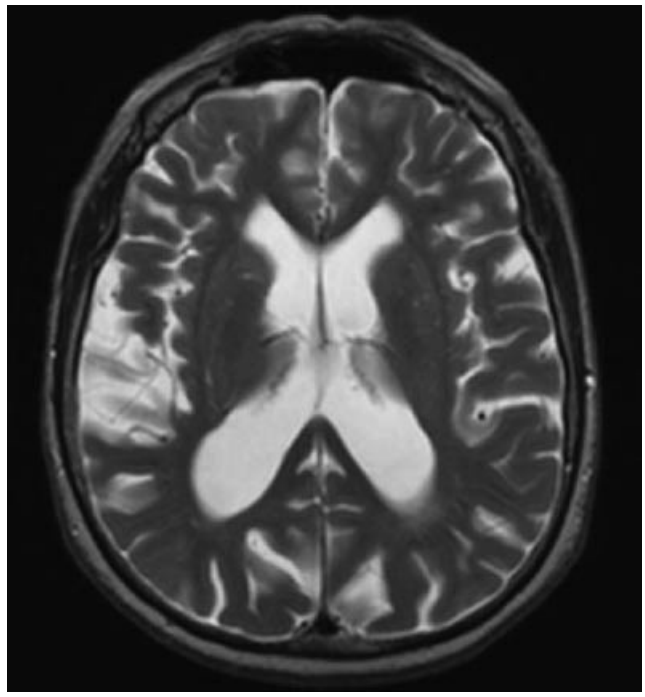


Figure 56.3 Natural *ex vacuo* dilatation of the ventricles as a result of ageing-related cerebral atrophy.

the brain, this *ex vacuo* phenomenon has to be taken into consideration when evaluating for hydrocephalus in the geriatric population. For it to be significant, the ventriculomegaly has to be out of proportion to cerebral atrophy (Figure 56.3).

Lumbar puncture

In many disease conditions, a lumbar puncture (LP) or spinal tap is routinely used to obtain CSF for laboratory studies. Its role is different in NPH; it is not so much for CSF sampling but rather CSF evacuation to see whether removal of CSF from a patient's system results in an improvement of symptoms, primarily gait. The other difference is that larger amounts of CSF evacuation are necessary in the evaluation of NPH as smaller volumes may not be sufficient to uncover potential benefits. It is therefore typically referred to as a high-volume LP to differentiate it from the usual LP where just enough is obtained for cell counts or culture. The amount of CSF removed varies but is usually around 40 ml. Although any competent physician may choose to perform the LP, it is commonly done by the neurologist, and for good reason. Aside from being technically skilled in the procedure itself, neurologists are in the best position to evaluate the character of a patient's gait before and after high-volume LP. For a more accurate comparison, many will videotape the patient walking pre- and post-LP. In patients who show response, there is usually a return to the pre-LP gait disturbance after a few weeks. This further solidifies the diagnosis.

Although CSF may be sent to the laboratory for other tests, it serves no purpose in the diagnosis of NPH. There are ongoing efforts to identify CSF biomarkers that would be helpful in the diagnosis of NPH, but none has been proven to be useful.[24] Measuring CSF pressure for NPH *per se* is also unnecessary since the value of LP is in boosting the diagnosis of NPH and indicating shunt responsiveness if there is subsequent improvement in gait. Several studies have highlighted the high predictive value of a positive lumbar puncture test.[25–27] There are doubts, however, about how well this test identifies candidates for ventriculoperitoneal (VP) shunting, because the amount of CSF removed in this one-time process can be inadequate in producing neurological improvement. One can argue that LP does not closely mimic the continuous drainage of shunting. Some worry that there could be patients who show no gait improvement after this momentary drainage of CSF and potentially lose out on benefiting from a shunt. Hence many still consider or at least discuss the option of shunt placement even if high-volume LP is equivocal or unrevealing, especially if clinical signs and symptoms are typical for NPH. Others would advocate a more detailed and involved test such as a lumbar drain trial (see below). Still, LP continues to be the mainstay in identifying appropriate shunt candidates. It is available anywhere and is logistically simple to administer.

Lumbar drain trial

To mimic better the potential effects of a shunt, many have moved on to performing a lumbar drain (LD) trial rather than just relying on an LP. LD involves performing a lumbar puncture using a large-bore Touhy needle followed by insertion of a small-calibre catheter. The catheter is left in place to drain CSF continuously from the thecal sac for ~4 days. The catheter is connected to an external bag within a closed system that on average drains about 100–150 ml of CSF per day. Unlike LP, this is an in-house procedure and is usually under the care of the neurosurgery service. The patient stays in the hospital for the duration of the LD trial and is checked daily for improvement in gait and cognitive function. Typically, a third-party person such as a physiatrist or neurologist is in charge of the daily assessment so as to minimize bias. The choice between doing an LP or an LD trial varies across institutions not only due to differences in physician beliefs but also for logistical reasons such as bed availability for this type of non-urgent admission. Some patients also do not tolerate LD well. It may need to be aborted if there is significant spinal or low-pressure headache or nerve root irritation by the catheter causing back or leg pain.

LD has been shown to predict the surgical outcome in up to 100% of cases.[28,29] However, most would give an estimate that is closer to 80%. A prospective multicentre study found that a positive lumbar drain test predicted good shunt response in 87% of cases, but cautioned that a negative result in the test is unreliable as the false-negative rate was 64%.[27] Therefore, patients who have a negative lumbar drain test should still be considered for shunting and one should look at the overall clinical picture and the patient's wishes as guides in the decision-making process.

Lumbar or CSF infusion test

The lumbar or CSF infusion test is not a widely used diagnostic tool but has its own advocates. It is a hydrodynamic test that is performed by inserting two cannulas into the lumbar thecal sac, with one cannula attached to an infusion pump and the other to a closed-system pressure monitor. A similar manoeuvre can be done intraventricularly through a surgically placed ventricular access device, but this is less popular as it is more invasive. The test assesses CSF absorption on the premise that the pathology lies in increased resistance to CSF outflow. Normal saline is infused at a constant rate until a steady-state intracranial pressure (ICP) plateau is reached. A value for resistance to CSF outflow, commonly denoted RCSF, is then calculated by dividing the increase in pressure during infusion by the infusion rate.[30] RCSF values below 13 mmHg ml^{-1} min^{-1} are regarded as normal[31] whereas values above 18 mmHg ml^{-1} min^{-1} are abnormal.[32] The positive predictive value has been estimated to be 80% and its false-negative prediction is about 16%.[33] There has been some argument about the details of the equation used to calculate RCSF[34] and also on what absolute value predicts good response to shunting. There are some who feel that the infusion test is of no value in diagnosing NPH.[23] Although the infusion test may be useful, it is not widely employed because it is cumbersome and relatively invasive, with equivalent information that can be obtained with other tests such as the lumbar drain.

Flow within the aqueduct

CSF flow characteristics in the aqueduct of Sylvius can be studied using MRI. Bradley *et al*.[35] found that increased flow void in the aqueduct, as seen on proton density-weighted conventional spin-echo images, was associated with better shunt outcome. Phase-contrast MRI is able to demonstrate CSF movement within the aqueduct during the cardiac cycle. This has been termed aqueductal CSF stroke volume and a finding of hyperdynamic flow correlates well with good response to surgery.[36,37] Although high aqueductal CSF flow is a good predictor of a favourable outcome, a finding of normal velocity should not be interpreted as ruling out NPH.[38] In such instances, further evaluation with other tests needs to be done. It should be mentioned that there have been dissenting opinions on the usefulness of CSF flow rate analysis. One such study showed that measurement of aqueductal CSF flow was not reliable in predicting post-shunt improvement.[39] Likewise, it has been shown that whereas a high CSF flow rate was associated with a good shunt response, the postoperative flow rate was unpredicatable.[40]

ICP monitoring

ICP monitoring has been shown to have some use in NPH. However, it is not the absolute ICP value but rather ICP pulsatility that has clinical significance. A recent study showed that patients who underwent ICP monitoring and were found to have abnormal ICP pulsatility had a 93% response rate to surgery, whereas those who had normal ICP pulsatility had only a 10% surgical response rate.[41] Abnormal ICP pulsatility was defined as an average ICP wave amplitude of >4 mmHg and >5 mmHg in more than 10% of recording time. It also showed that static ICP measurements were not good at predicting surgical outcome. Other investigators have shown that the presence of B waves, which indicate normal mean baseline ICP with transient elevations of mean and pulse pressure, in more than half of the monitoring points to a better outcome with shunting.[42,43]

Neuropsychological testing

Of the clinical triad, the cognitive dimension is probably the most challenging to study. Neuropsychologists, therefore, play an important role in helping complete the clinical picture of an NPH patient. Neuropsychological testing not only assists in the pretreatment diagnosis but is also valuable in outcome assessment and long-term follow-up. It involves a detailed, multifaceted study, but visual attention, verbal recall and motor precision appear to be the most representative tests.[44] Although some have expressed doubts about the value of neuropsychological testing in diagnosing NPH and in outcome prediction, its use has grown and most institutions with formal programmes for NPH employ it to detail the cognitive impairment in NPH. It may even differentiate between signs of NPH and mild Alzheimer's disease.[45]

Other tests

There are other tests that have been used to help in the diagnosis of NPH. In a review of non-invasive biomarkers in NPH, investigators found three diagnostic studies that correlated well with surgical outcomes.[46] These are phase-contrast MR imaging showing CSF flow void (as discussed earlier), magnetic resonance spectroscopy (MRS) and single-photon emission computed tomography (SPECT). An Alzheimer-type pattern on SPECT and a typical *N*-acetylaspartate/choline ratio on MRS were found to predict surgical response with high accuracy. However, these diagnostic modalities have yet to become standard in the workup for NPH as further studies are needed to support their true usefulness. Another diagnostic test that has been described is radionuclide cisternography. However, its results have been found to be poor predictors of response to shunting,[47] Positron emission tomography (PET) has also been investigated. It showed decreased regional glucose metabolism in patients with idiopathic NPH as a group, but there was no significant correlation with shunt outcome.[48] Still, PET has led some to focus attention on the thalamus and basal ganglia,[22] where mean cerebral blood flow has been found to be decreased in NPH patients[49]

Treatment

Patient selection and decision-making

Despite the numerous diagnostic modalities that have become available, patient selection for surgery starts with the recognition of clinical features of NPH coupled with evidence of ventriculomegaly on CT or MRI. The exact criteria for determining which patients to operate on vary from institution to institution. Indeed, it can even vary from one surgeon to the next within the same institution. The establishment of formal NPH programmes has helped reduce some of the variability and the occasional accompanying confusion. At one author's institution, a candidate undergoes neuropsychological evaluation and a large-volume LP. We used to insist on a lumbar drain trial but it became problematic for logistical reasons such as bed availability for these low-priority elective admissions. We have, therefore, relied on response to the LP as an indicator for surgery. When response is equivocal, we still consider a lumbar drain trial for further delineation. At the other institution, the lumbar drain trial is employed to select who will most likely benefit from surgery.

In places where the CSF infusion test is employed, experts recommend a cutoff value of 18 mmHg ml^{-1} min^{-1} on outflow resistance, whereas those with values below 18 mmHg ml^{-1} min^{-1} may also be shunted if their CT shows typical findings of NPH with limited white matter lesions and no significant cerebrovascular disease on history.[50] There are a number of other ancillary tests that may be useful, but these are either not widely accepted or not easily available. Indeed, of all the diagnostic modalities that have been discussed above, no single test can rule out potential response to surgery.[51] This has led some to realize that we may be too rigid and conservative about whom to offer surgery, especially since the procedure involved is relatively low risk. In an interesting study entitled 'Shunts in normal pressure hydrocephalus: do we place too many or too few?', it was calculated that even if half of all shunted patients develop complications, the response rate to shunting would have to be less than 5% for the procedure to do more harm than good.[52] Other studies support advocacy towards a lower threshold for offering shunt placement to patients with suspected NPH in the hope of reducing the number of patients who may miss out on the life-changing benefits of shunt placement.

Ventriculoperitoneal shunting

The mainstay of NPH treatment is CSF diversion in the form of VP shunting. The shunt system has three basic parts: (1) the ventricular catheter, also referred to as the proximal catheter; (2) the valve, which regulates flow and may have an associated reservoir for CSF tapping; and (3) the peritoneal catheter, also known as the distal catheter (Figure 56.4). Basically, the shunting procedure involves inserting the proximal catheter into the lateral ventricle and connecting it to the reservoir-valve unit. This unit, in turn, is connected to the distal catheter which drains into the peritoneal cavity where the CSF is absorbed along its lining. Some wonder whether this will cause the abdomen to bloat, but in reality, unless the peritoneum has a malabsorption problem, the patient will not notice a change because the amount of CSF coming out of the distal tip is actually an intermittent trickle and not a continuous outpour. The

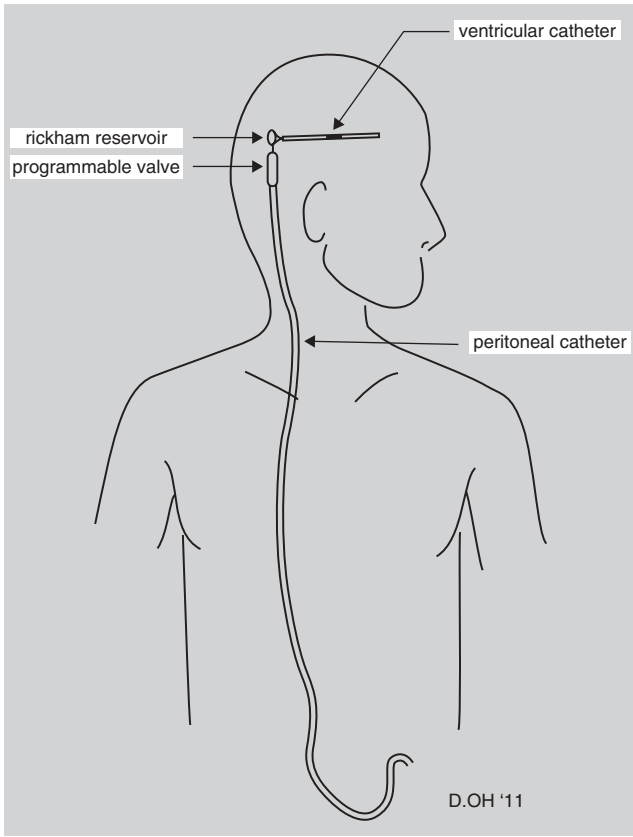


Figure 56.4 Diagram of a ventriculoperitoneal shunt system.

valve and reservoir are implanted in subgaleal space, easily palpable so that the valve can be readily reprogrammed using a hovering magnet and the reservoir can be tapped with a gauge 23 or 25 needle. A CSF or shunt tap is done when CSF samples are needed for studies or the patency of the shunt system needs to be tested.

The ventricular catheter is placed through an occipital or frontal burr hole and the rest of the shunt system is threaded down the side of the neck and anterior chest wall in the subgaleal–subcutaneous layer with the aid of a tunnelling device. The patient is left with two just two small incisions, one in the scalp and another on the abdominal wall. Alternatively, the distal catheter may be implanted into the pleural cavity or the atrium of the heart if the peritoneum is not a viable place for CSF absorption or was a site of previous failure. The operation is done under general anaesthesia and usually lasts about 30–60 min. It commonly entails a one-night stay in the hospital.

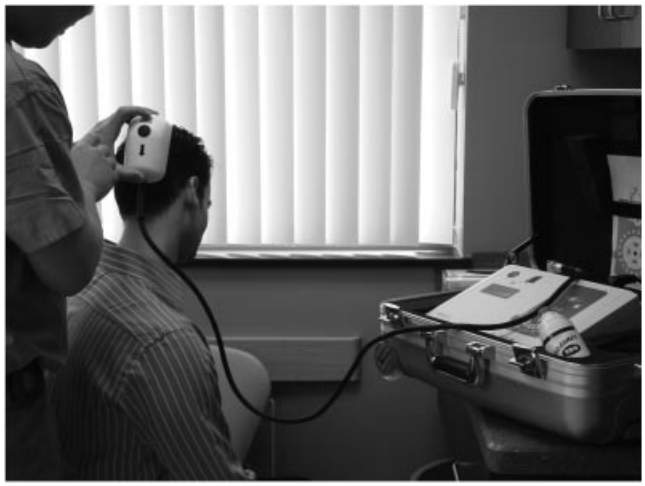
Programmable valves

The catheters used are standard but there is considerable variation in the type of flow-regulating valve. Conventionally, shunt systems employ valves that come with preset opening pressure levels – low, medium and high. Low-pressure valves allow CSF to pass through even at low CSF pressures whereas high-pressure valves allow CSF drainage only when CSF pressures are high enough. In NPH, where the CSF pressure is not typically elevated, patients do well with low- and medium-pressure valves. However, there are times when a higher resistance to drainage is necessary. This is most commonly encountered in cases where overdrainage from the ventricles inside the brain leads to a relative shrinkage of the brain surface away from the dura and causes the formation of subdural effusions or haemorrhage. Patients have had to be taken back to the operating room to change the valve to a high-pressure one to drain less CSF, allow brain re-expansion and make the subdural effusion go away.

It therefore became apparent that finding the right balance between CSF drainage and overdrainage is not something that is best addressed by fixed-pressure valves. Patients also tend to find optimal gait at different valve settings. For this reason, programmable or adjustable shunt valves were developed and have become widely used in the treatment of NPH. As an example, we can look at the most commonly used version, which is the Codman–Hakim programmable valve. It has a pressure setting range of 30–200 mmH_2O and can be adjusted in increments of 10. At the time of surgery, the valve is typically programmed to an initial setting of 120 mmH_2O. Postoperatively and in subsequent clinic visits, the valve setting can be adjusted, according to the patient's progress, by simply holding up a magnetic programmer over the shunt valve (Figure 56.5). It therefore eliminates the need for a reoperation in cases of overdrainage or underdrainage, and allows us to find the optimal pressure setting for a particular patient. As a demonstration of how useful the programmable shunt is, one study showed that about half of shunted patients required adjustments.[53] The reprogramming was downward in 52% of cases for underdrainage (Figure 56.6) and upward in 46% for overdrainage and subdural haematoma formation. The ability to programme and reprogramme the shunt valve is an extremely useful advantage, not only in the immediate postoperative period but also in later years, as a particular patient who does well at a certain pressure level may later require a different setting as his or her intracranial dynamics change over time.

Endoscopic third ventriculostomy

Although VP shunting is the standard treatment for NPH, it is not the only way of diverting CSF from the ventricles. Endoscopic third ventriculostomy (ETV), a well-established procedure for hydrocephalus in children, involves creating a hole in the thin, membranous floor of the third ventricle with the use of a neuroendoscope, which is introduced through a frontal burrhole. It takes advantage of



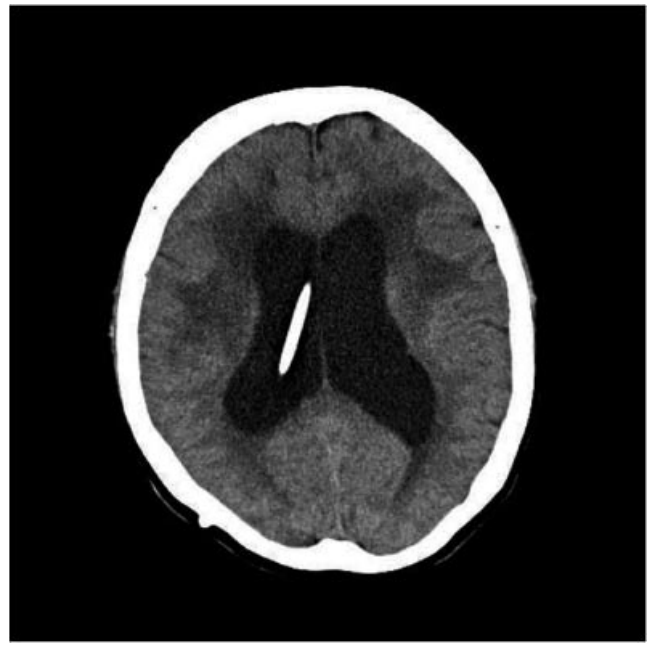
(a)

(b)

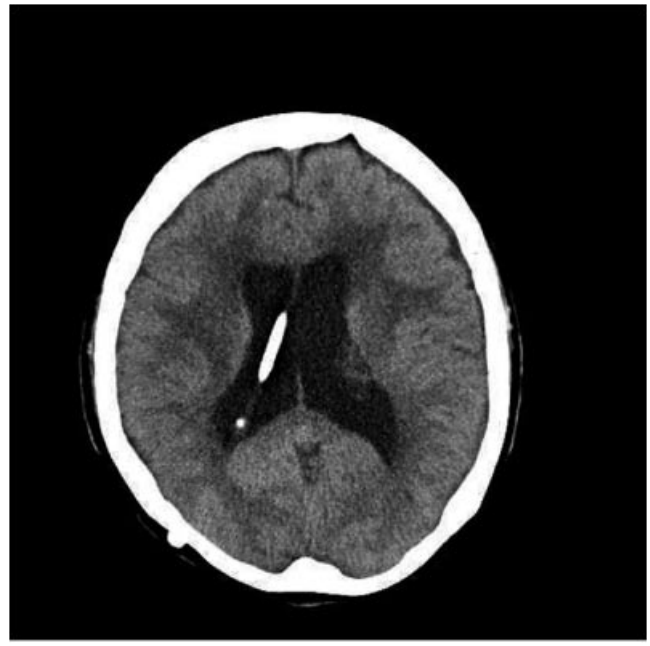
Figure 56.5 Valve pressure programming for the Codman–Hakim shunt. The newer version has a built-in ultrasound tip that automatically verifies the new setting which saves having to send the patient for X-ray verification after each adjustment.

an interesting and unique anatomical feature of the CSF pathway, that is, this thin floor is all that separates the CSF being produced in the upper ventricles from the basal subarachnoid space beneath where CSF is eventually absorbed. Hence this allows CSF to bypass the aqueduct of Sylvius, fourth ventricle and the foramina of Magendie and Luschka and gets it straight to arachnoid villi for absorption. It does away with having to leave any hardware in the body and with it shunt-related complications such as malfunction or infection are avoided. It is a safe procedure and is as short as a standard shunt operation.

It is easy to imagine how ETV works well for children with aqueductal stenosis or other forms of obstructive hydrocephalus. Indeed, it has been shown to be useful in NPH especially if aqueductal stenosis is the underlying



(a)



(b)

Figure 56.6 Ventricles do not necessarily get smaller after successful shunting where there is good clinical response. However, a decrease in ventricular size/hydrocephalus and in overall brain 'tightness' can sometimes be demonstrated on imaging. In this figure, the change was seen after lowering the pressure setting of a programmable valve.

cause. However, the question that is raised when applied to idiopathic NPH is whether ETV does any good given that the problem is not an obstruction in the aqueduct, fourth ventricle or foramina; it is a form of communicating hydrocephalus.

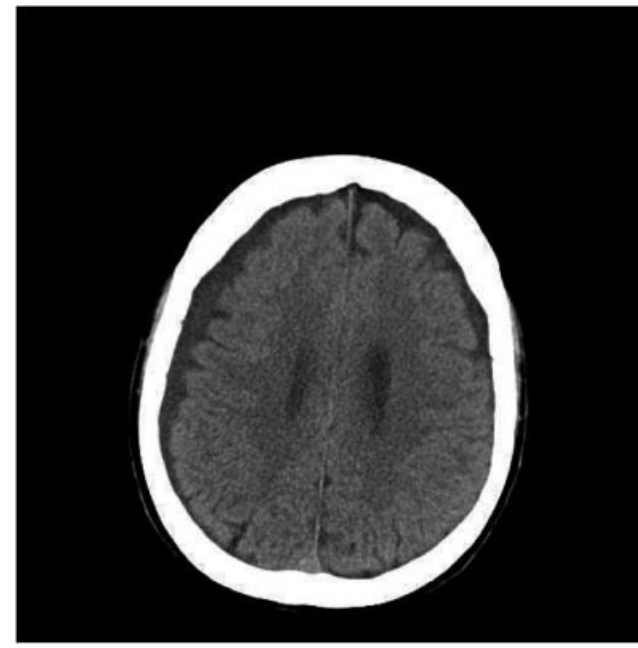
The argument is that the impedance is downstream at the level of the arachnoid villi. However, there is evidence that it can be effective in NPH, with reports suggesting that ETV works by relieving stress along the periventricular tissue and improving local blood flow.[54] Some use ETV in NPH patients whose outflow resistance is increased in the ventricular infusion test but not in the lumbar infusion test, a finding that suggests functional aqueductal stenosis.[55] Recent literature espousing the hydrodynamic theory gives further credence to the effectiveness of ETV in treating NPH, as discussed earlier in this chapter.

Risk and complications

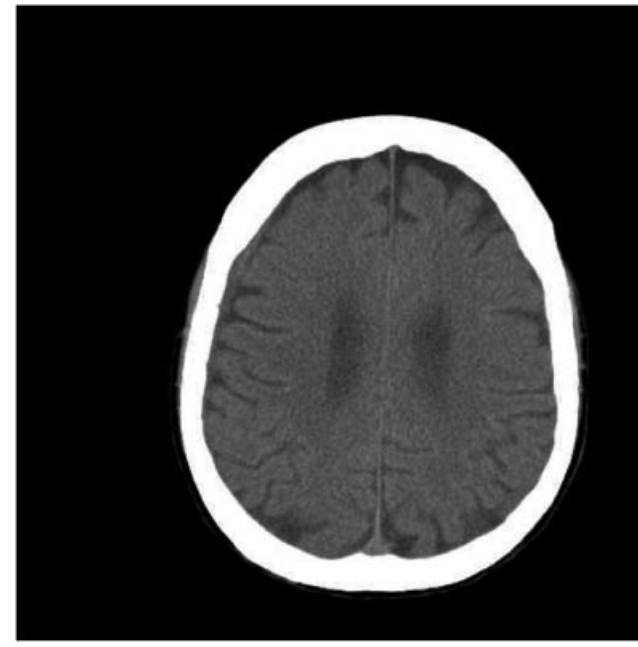
A shunt operation is generally safe, but just as with any operation in the elderly, systemic complications may occur. With reference to the shunt, there is a 1–2% risk of perioperative bleeding or infection. Late shunt complications are also possible. In fact, these are among the most frustrating problems in neurosurgery, although they do not appear to be nearly as common in the adult population as in the paediatric realm. Still, one systematic review of studies on NPH spanning the period 1977–2000 revealed an overall complication rate of 38% and a reoperation rate of 22%.[47] More recent data, however, show lower complication rates of 14–20%,[53,56] reflecting benefits gained through advances in techniques and materials. Furthermore, the advent of programmable valves has made many of these cases readily solvable without having to take the patient back to the operating room.

Shunt infection presents as fever and/or erythema and tenderness along the shunt tract. In severe cases, there can be skin breakdown and discharge of purulent material. It is verified by CSF cell counts and positive cultures obtained through a shunt tap. The optimum treatment for shunt infection is externalization of the distal catheter usually at the level of the clavicle for about 1 week while antibiotics are given to treat the infection. If the patient is not too shunt dependent, it can simply be removed. After the infection clears, the shunt is then re-internalized with a new distal catheter or an entirely new system is installed.

Subdural effusions appear as hypodense collections on CT and T1 hypointense collections on MRI over the cerebral hemispheres. They can sometimes be watched, usually if they are less than 1 cm in thickness. If the shunt is a programmable one, the pressure setting can be raised to obliterate the subdural collection (Figure 56.7). Although not all subdural collections have to be addressed and may actually coexist with improved CSF dynamics and



(a)



(b)

Figure 56.7 Subdural effusion. Note the hypodense collection in the subdural space (a). After increasing the pressure setting of the programmable valve, which decreases the amount of CSF drained from the ventricles and leads to brain re-expansion, subdural effusion is resolved (b).

good clinical response,[57,58] those that are persistent and symptomatic have to be surgically drained.

Shunt obstruction is another complication that may occur, although the rate is again notably lower than in the paediatric shunt population. It is usually due to proteinaceous debris or blood products clogging up the ventricular catheter, valve chamber or distal catheter. This may be checked by doing a shunt tap, as previously mentioned, which allows evaluation of shunt patency. A radionuclide study can also be done to check shunt patency when shunt obstruction is suspected.[59] Any part of the catheter may also fracture or become disconnected for reasons such as trauma or simple wear-and-tear over time. This can be revealed by X-rays that show the entire shunt system, commonly referred to as a *shunt series*. Reoperation involves identifying the malfunctioning component and then either flushing or replacing it.

An intriguing complication is hearing loss. Subjective note of post-shunt hearing loss is not common, but a study actually showed that two-thirds of ears tested showed a loss of more than 10 dB after shunting.[60] Most of it was temporary, however, and recovery was seen within a few months. The cause remains unknown.

ETVs are not without problems. It should be noted that not all neurosurgeons may be comfortable performing it. ETV may be technically challenging for someone who does not perform it routinely. Intraoperative complications include intraventricular haemorrhage and vascular injury in the prepontine cistern upon advancement of the endoscope through the floor of the third ventricle. While shunt-related problems are avoided, ETV may also fail at a later time as the hole in the third ventricular floor can spontaneously close. A repeat ETV may be performed or conversion to a VP shunt may be offered.

Outcome and prognosis

Response rates following VP shunting vary not so much based on the surgical prowess but rather patient selection. It is therefore important that we identify surgical candidates based on predictors of good outcome. These include the presence of the classic clinical features of NPH, an unequivocally positive result on lumbar puncture or lumbar drain trial and the presence of pressure signs on CT or MRI such as periventricular transependymal flow. We also rely on clinical acumen in delineating the character of a patient's gait to see how suggestive it is for NPH. CSF outflow resistance values of more than 20 mmHg ml^{-1} min^{-1} and the absence of dementia have also been correlated with good outcome in patients with late-stage NPH.[61] For patients undergoing continuous ICP monitoring, the presence of B waves in more than 50% of the recording time predict good outcome.[43] Factors that do not appear to affect outcome were patient's age, duration of symptoms, extent of ventricular dilatation and degree of dementia.[56]

The generally accepted success rate of VP shunting for NPH is 80%. In terms of symptom components, improvement is commonly seen in gait and urinary incontinence, but not as consistently in cognitive impairment, particularly short-term memory. Studies estimate that 81–86% of patients improve in gait, 70% in bladder control and 40–44% in cognitive function.[39,56] Sustained long-term improvement is more difficult to measure, as some patients who initially do well after shunting may experience deterioration in later years. However, this problem has been greatly reduced with the use of programmable valves. As the mechanical characteristics and CSF flow dynamics of a patient's brain change over time, reprogramming the valve setting can help in establishing a favourable flow soon after or long after surgery without the need for a reoperation. Shunt devices are designed to last a long time and they usually last a lifetime. Replacement is only necessary when it is clogged, fractured or infected. The survival rate of shunt devices in general is 50% in 5 years whereas for programmable valves it has been estimated to be around 80% in 5 years.[53]

Long-term care and follow-up

Most patients readily recover their functions after surgery. For some, however, rehabilitation is an essential component of the recovery process. Physical therapy can be performed in a rehabilitation centre or at home, depending on how well the patient does after surgery and how much social support is available. As discussed above, there is a period after shunt placement when the shunt valve is reprogrammed based on the patient's clinical performance until the optimal setting is found. Once this has been achieved, the patient is usually followed once per year with a CT scan. Of course, patients are advised to seek immediate attention if any problem occurs in the interim. The CT scan is not so much for monitoring ventricular size, which may or may not change after shunting, but more for checking for formation of subdural collections or other sequelae. The patient may also need to be seen at times when he or she undergoes an MRI for any body part, as being in a strong magnetic field can alter the pressure setting of a programmable shunt valve. We will typically check the valve setting by taking an X-ray of the valve and looking at its dial or simply reprogramme it to the intended setting with ultrasonic confirmation.

Neurologists are typically involved in the initial workup for NPH, but there is now greater recognition of the unique role that they can also play in its long-term management.[18] Their understanding of other similar neurological conditions and how these may overlap or interact with NPH allows for optimal follow-up and guidance of management in partnership with neurosurgeons, geriatricians and other providers.

Key points

- In an older patient with symptoms and signs of gait disturbance, change in mental performance and urinary dysfunction, normal pressure hydrocephalus (NPH) should be considered as a possible diagnosis.
- Imaging via computed tomography (CT) or magnetic resonance imaging (MRI) remains the main diagnostic tool in NPH.
- Ventriculoperitoneal (VP) shunting appears to be successful in about 80% cases of NPH.

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CHAPTER 57

Acute stroke care and management of carotid artery stenosis

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Introduction

A stroke is defined as 'rapidly-developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 h or until earlier death, with no apparent non-vascular cause' by the World Health Organization.[1] A stroke is therefore distinguished from a transient ischaemic attack (TIA), which is defined similarly, except that the focal neurological symptoms must recovery fully within 24 h. The term 'cerebrovascular accident' should be avoided because of its negative connotations. Stroke carries with it a significant personal, community and economic burden. It is estimated that, in the USA alone, around 795 000 patients suffer a stroke each year at a direct and indirect financial cost of over US$70 billion.[2] When considered separately from other cardiovascular diseases, stroke is the third leading cause of death in the Western world, and in the world as a whole it is the second commonest cause of death. It is also the leading cause of disability in survivors. Stroke occurs at all ages from birth onwards, but becomes increasingly common with increasing age and is a major cause of suffering in the elderly population.

The management of acute stroke is evolving and applied evidence from recent randomized controlled trials, along with better management of associated risk factors, has contributed to a relative reduction in age-adjusted morbidity and mortality from the condition in many countries. There now exists a good evidence base for hyperacute and acute interventions, and also for pharmacotherapy with the aim of secondary prevention. Acute stroke will, however, remain an important and common medical presentation as the proportion of the population aged over 65 years increases in many developed countries.

This chapter addresses the aetiology of stroke, the immediate management of the patient presenting with an acute stroke, the initiation of secondary prevention measures and the management of carotid artery stenosis. Intracerebral and subarachnoid haemorrhage are also discussed, as these conditions will also present to the geriatrician or stroke physician with the rapid onset of a focal neurological deficit.

Stroke aetiology

It is important to recognize that the terms 'stroke' and 'TIA' describe the presentation of the patient and are not sufficient as a diagnosis on their own. This requires a description of the underlying pathology (haemorrhage or infarction), anatomy (vessel and territory involved) and aetiology (mechanism). Ischaemic stroke may occur as a result of a number of heterogeneous conditions. The major precipitant of cerebral ischaemia in the elderly population is atherosclerosis. Atheromatous plaque may occlude the artery at the site of buildup, but more commonly plaque rupture with superimposed thrombosis results in occlusion or embolization to a smaller, more distal artery, precipitating cerebral ischaemia. Smaller 'lacunar' infarcts may be caused by microatheroma of the deep penetrating arteries of the brain or by hyaline degenerative disease of the arterioles, which together are known as small-vessel disease. The pathogenesis of atherosclerosis is discussed in more detail later in this chapter. Alternatively, stroke may be caused by intracranial haemorrhage, cerebral venous thrombosis or cardiac embolism.

Cardiac embolism may arise from thrombus formation in the left atrium promoted by arrhythmia (especially atrial fibrillation or flutter), valvular heart disease or valve prosthesis or in myocardial infarction where mural thrombosis may develop on the injured myocardium. An inter-atrial or inter-ventricular septal defect (e.g. patent foramen ovale) may allow the passage of an embolus from the venous circulation to the left side of the heart, with the potential for subsequent paradoxical embolization to the cerebral vessels.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 57.1 Classification of causes of stroke.

Cerebral infarction

Extracranial arterial embolism (internal carotid artery, aorta or vertebral artery)
- Atherosclerosis, arterial dissection, fibromuscular dysplasia, vasculitis, arterial trauma

Cardiac embolism
- Mural thrombus following myocardial infarction, rheumatic heart disease, calcific or prosthetic mitral or aortic valves, endocarditis, atrial fibrillation, atrial myxoma

Paradoxical embolism
- Deep vein thrombosis with atrial septal defect

Trauma
- Fat embolism

Iatrogenic embolism
- Cardiac surgery, cardiac catheterization, cerebral angiography

Intracranial arterial thrombosis
- Large-vessel occlusion – atherosclerosis, vasculitis, dissection, hypercoagulable states, sickle cell disease, Moyamoya disease
- Small-vessel occlusion – hypertensive arteriosclerosis, diabetes, CADASIL, vasculitis

Vasospasm
- Subarachnoid haemorrhage

Haemodynamic ischaemia
- Internal carotid artery occlusion, tandem stenoses, bilateral vertebral arterial occlusion, systemic hypotension (e.g. cardiac arrest), severe stenoses with poor collateral supply

Cerebral venous thrombosis
- Hypercoagulable states, puerperium, intracranial sepsis, malignancy

Intracranial haemorrhage

Subarachnoid haemorrhage
- Aneurysm, arteriovenous malformation, bleeding disorders, vascular malignancies, vasculitis, illegal drug use

Intracerebral haemorrhage
- Cerebral amyloid angiopathy, cavernous angioma, hypertensive small-vessel disease, cerebral venous thrombosis, venous anomalies and other causes as for subarachnoid haemorrhage

A number of other conditions may either cause ischaemic stroke or mimic its signs and symptoms and should be considered in the differential diagnosis. Information from history, examination and investigation pointing to an alternative cause should be pursued vigorously, as the appropriate and timely management of the underlying pathology may alter the chance of recurrent disease (Table 57.1).

Stroke mimics

Conditions that may mimic stroke but that are not of vascular origin include space-occupying lesions (e.g. subdural haematoma, tumour or abscess), hypoglycaemia, functional disorders and epilepsy, especially post-ictal paresis (Table 57.2).

Table 57.2 Differential diagnosis – stroke 'mimics'.

Traumatic
- Subdural haematoma
- Head injury

Metabolic
- Metabolic encephalopathy
- Toxic encephalopathy
- Hypertensive encephalopathy
- Hypoglycaemia

Structural
- Cerebral tumour
- Arteriovenous malformation

Infective
- Focal encephalitis
- Cerebral abscess

Functional

Genetic disorders
- Familial periodic paralyses
- Mitochondrial encephalopathy
- Porphyria

Disorders of neural and neuromuscular function
- Epileptic seizure and post-ictal neurological deficit
- Multiple sclerosis
- Central pontine myelinolysis
- Acute polyneuropathy
- Myasthenia gravis
- Motor neurone disease

Prognosis of stroke

The mortality following first ischaemic stroke may be as high as 41% after 5 years,[3] with vascular causes of death (stroke and myocardial infarction) most common during the first few weeks following the event.[3] The risk of recurrent stroke is highest in this acute period. When patients are divided into groups depending on the aetiology of their stroke, those with significant large-artery (carotid) atherosclerosis are at highest risk of recurrence within the first month. Recurrence is least likely in those with small-vessel disease as a cause of their stroke.

Clinical evaluation and stroke syndromes

Evaluation of the patient should begin with a detailed history. In the case of the aphasic, obtunded or confused patient, a witness history should be obtained from the ambulance staff, relative, friend or carer. It is important to establish the exact time of onset of symptoms, the

progression or regression of a deficit over time and any associated features such as headache, loss of consciousness or possible seizure. Important details from past medical history will be the presence of other cardiovascular, neurological or haematological disease, medications taken, family history and ascertainment of risk factors. It is important to establish the patient's baseline social function with respect to activities of daily living to plan future treatment, including resuscitation status, and also rehabilitation.

Examination should focus on establishing the nature and severity of the neurological deficit to aid in confirming the clinical diagnosis of stroke and establishing the likely site and size of cerebral lesion. Examination of other systems, especially the heart, may give clues to an underlying cause or prompt further investigation.

The severity of neurological deficit should be assessed using a formal tool such as the National Institutes for Health (NIH) Stroke Severity (NIHSS) Score.[4] This examination should be performed at the time of presentation and grades the patient response in a number of domains, which comprise level of consciousness, gaze and vision, motor power, ataxia, language and speech and extinction and inattention, using specific validated techniques of examination. Higher scores are associated with more profound deficit and worse outcome, although the prominence of language domains in the score may underestimate the severity of the impact of right hemispheric syndromes. The NIHSS score is used to select patients for thrombolysis (see below) and monitor their early progress. Other scales, including the Barthel Index[5] and modified Rankin score[6] (Tables 57.3 and 57.4), grade disability and handicap and are used to guide rehabilitation and measure the progress or outcome of treatment.

Identifying the likely size and location of the arterial territory involved from the symptoms and signs is an important aid to determining the mechanism and prognosis of stroke. The commonest arterial syndromes are described in the next section. Occlusion and rupture of vessels (i.e. infarction or haemorrhage) result in similar syndromes, which are indistinguishable clinically. However, in the next section, the description concentrates on ischaemic stroke for simplicity.

Table 57.3 The Barthel Index.[5]

	Bowels
0	Incontinent (or needs to be given enemata)
1	Occasional accident (once per week)
2	Continent
	Bladder
0	Incontinent or catheterized and unable to manage
1	Occasional accident (maximum once per 24 h)
2	Continent (for over 7 days)
	Grooming
0	Needs help with personal care
1	Independent face/hair/teeth/shaving (implements provided)
	Toilet use
0	Dependent
1	Needs some help, but can do something alone
2	Independent (on and off, dressing, wiping)
	Feeding
0	Unable
1	Needs help cutting, spreading butter, etc.
2	Independent (food provided within reach)
	Transfer
0	Unable – no sitting balance
1	Major help (one or two people, physical), can sit
2	Minor help (verbal or physical)
3	Independent
	Mobility
0	Immobile
1	Wheel chair independent including corners, etc.
2	Walks with help of one person (verbal or physical)
3	Independent (but may use any aid, e.g. stick)
	Dressing
0	Dependent
1	Needs help, but can do about half unaided
2	Independent (including buttons, zips, laces, etc.)
	Stairs
0	Unable
1	Needs help (verbal, physical, carrying aid)
2	Independent up and down
	Bathing
0	Dependent
1	Independent (or in shower)
Total	(0–20)

Total middle cerebral artery (MCA) syndromes

Occlusion of the trunk of the middle cerebral artery (MCA) carries the gravest prognosis and may cause infarction of a large area of brain tissue supplied by its superficial cortical branches and the deep lenticular branches supplying basal ganglia and internal capsular white matter. There is cortical dysfunction (such as a speech or spatial disorder depending on the hemisphere involved), motor and/or sensory deficit of the face and arm or arm and leg and homonymous visual field defect. There may also be a decreased level of consciousness secondary to oedema and brainstem compression, which usually develops over the course of the first 24–48 h after onset. Total MCA territory infarction is frequently fatal, with a 1 year mortality of up to 40%, depending partly on the care provided.[7]

Table 57.4 The Modified Rankin Score.[6]

Grade[a]	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention

[a] In clinical trials, a grade of 6 is often added to record patients who have died.

Partial MCA syndromes

Branch occlusions of the MCA are heterogeneous in their presentation. If the upper division of the MCA is affected, then typically there is no visual field defect. If the lower division of the MCA is affected, then typically there is a reduced motor or sensory component to symptoms and signs. Branch occlusion is more commonly caused by embolism than local thrombus. Prognosis is variable, with a 1 year mortality of up to 16%, but 55% of patients are independent at 1 year.[7]

Lacunar syndromes

Occlusion of small perforating arterioles supplying the basal ganglia, external or internal capsule and the pons results in small infarcts known as lacunes. These have been defined on brain imaging as deep subcortical infarcts less than 15 mm in maximum diameter. They are caused by occlusion of the smaller perforating arteries either secondary to microatheroma at the vessel origin or secondary to more distal lipohyalinosis in which degenerative pathological changes occur in the tunica media and adventitia of the vessels. These two pathologies are difficult to distinguish clinically or radiologically and together are often known as *small-vessel disease*. This term is also frequently used by radiologists to describe the appearances of patchy or confluent low attenuation on computed tomographic (CT) or high signal on T_2 and fluid-attenuated inversion–recovery (FLAIR) magnetic resonance imaging (MRI) scans, in the periventricular deep white matter. These changes are also known as leukoaraiosis and are thought to be another manifestation of lipohyalinosis, as are microhaemorrhages seen on gradient echo (T_2*) MRI. Leukoaraiosis, lacunes and microhaemorrhages are independently associated with cognitive impairment. Hypertension is a major risk factor for lacunar infarction, leukoaraiosis and microhaemorrhages. The last are also associated with cerebral amyloid angiopathy.

Four common presentations of lacunar infarction, known as lacunar syndromes, are described. Pure motor stroke presents with unilateral face, arm and leg weakness. The weakness may not involve all three sites, but should involve at least two contiguous sites, that is, face and arm or arm and leg. Pure sensory stroke gives rise to hemisensory loss on the contralateral side. A larger infarct may give rise to a mixed motor/sensory stroke, but the characteristic feature of lacunar infarction remains, which is that there is no disturbance of higher (cortical) function and no visual field deficit. The fourth common type of lacunar stroke, ataxic hemiparesis, describes limb ataxia in combination with a hemiparesis and/or dysarthria. These syndromes arise from lacunar infarction (or occasionally small haemorrhages) in either the internal capsule or the pons and imaging is required to distinguish these sites. Numerous rarer lacunar syndromes are described, including unilateral chorea and hemiballismus from lacunes in the basal ganglia.

Lacunar stroke carries a good prognosis for survival, with a 1 year mortality of about 10%, but 50% of survivors remain dependent.[7]

Posterior circulation syndromes

Vertebrobasilar (or posterior) circulation syndromes result from ischaemia of the brainstem, cerebellum and/or occipital lobes, and therefore the symptoms experienced are varied depending on the vessels and territories affected. Brainstem infarction from basilar artery or perforating vessel occlusion can result in cranial nerve dysfunction, eye movement disorders and/or nystagmus, with or without bilateral motor and/or sensory deficit. Pontine infarction secondary to basilar artery thrombosis may cause the 'locked-in' syndrome. This produces quadriplegia, but with preservation of eye movements and blinking which may facilitate communication. Occlusion of one of the posterior cerebral arteries results in hemianopia, while occlusion of both posterior cerebral arteries results in cortical blindness. In some patients, the posterior cerebral artery supplies the median temporal lobe, in which case the visual field defect may be accompanied by mild or, if bilateral, severe memory impairment (amnesia). In about 5% of individuals, the posterior cerebral artery is supplied by the ipsilateral internal carotid artery via a dominant posterior communicating artery. In such cases, occipital infarction and hemianopia may result from carotid disease.

Cerebellar infarction may result in gait ataxia, but not necessarily any other cerebellar signs. Occlusion of the posterior inferior cerebellar artery (PICA) may produce the characteristic lateral medullary (Wallenberg) syndrome.

This comprises vestibular dysfunction, ataxia, ipsilateral loss of pain and temperature sensation from the face, ipsilateral Horner syndrome and contralateral loss of pain and temperature sensation in the arm and leg. Dysarthria and dysphagia are not specific for brainstem lesions and can occur with any motor syndrome.

In contrast to anterior circulation syndromes, thrombosis of the basilar artery may be responsible for a higher proportion of strokes than embolism from a distant site. The 1 year mortality for posterior circulation infarction is 19%, with 62% of patients independent at 1 year.[7]

Thalamic syndromes

The blood supply of the thalamus is carried by branches of the vertebrobasilar system and also the tuberothalamic artery that arises from the posterior communicating artery. Thalamic nuclei participate in sensory and motor function, language, cognitive function, alertness, memory, mood and motivation.[8] Hence the clinical syndrome that results from thalamic infarction depends on the specific nuclei involved. Unilateral infarction may cause memory loss or confusion, language disturbance when the dominant hemisphere is affected and spatial deficit when the non-dominant hemisphere is affected. The *thalamic syndrome* describes the combination of contralateral sensory loss and hemiparesis associated with the development of distressing post-stroke pain in the affected limbs. Bilateral infarction of the thalamus may result in coma with subsequent severe amnesia.[8]

Prehospital care

In many countries where hyperacute stroke treatments such as thrombolysis are available, the spotlight of public health has fallen on the early recognition of stroke by both the general public and allied health professionals.

Validated clinical tools such as the FAST ('Face, Arm, Speech Test') screening test[9] allow paramedics and the public to identify symptoms of stroke and can allow triage to the correct facility with early warning of the patient's arrival. FAST instructs the user to evaluate facial movement, upper limb power and speech to identify a neurological deficit and paramedic findings on examination correlate well with subsequent examination findings by a trained physician. It may, however, be less sensitive for the detection of posterior circulation events,[9] which has led to the development of the ROSIER ('Recognition of Stroke in the Emergency Room') Scale, which incorporated a measure of hemianopia and may be more suitable for use by physicians in the emergency department. Prospective validation of this scale in 173 patients referred with suspicion of stroke showed sensitivity of 93% (95% CI, 89–97%) and specificity of 83% (95% CI, 77–89%) for the diagnosis of stroke.[10]

A number of other, similar, screening tools in Melbourne (MASS), Cincinnati (CPSS) and Los Angeles (LAPSS) have also been described in the literature.

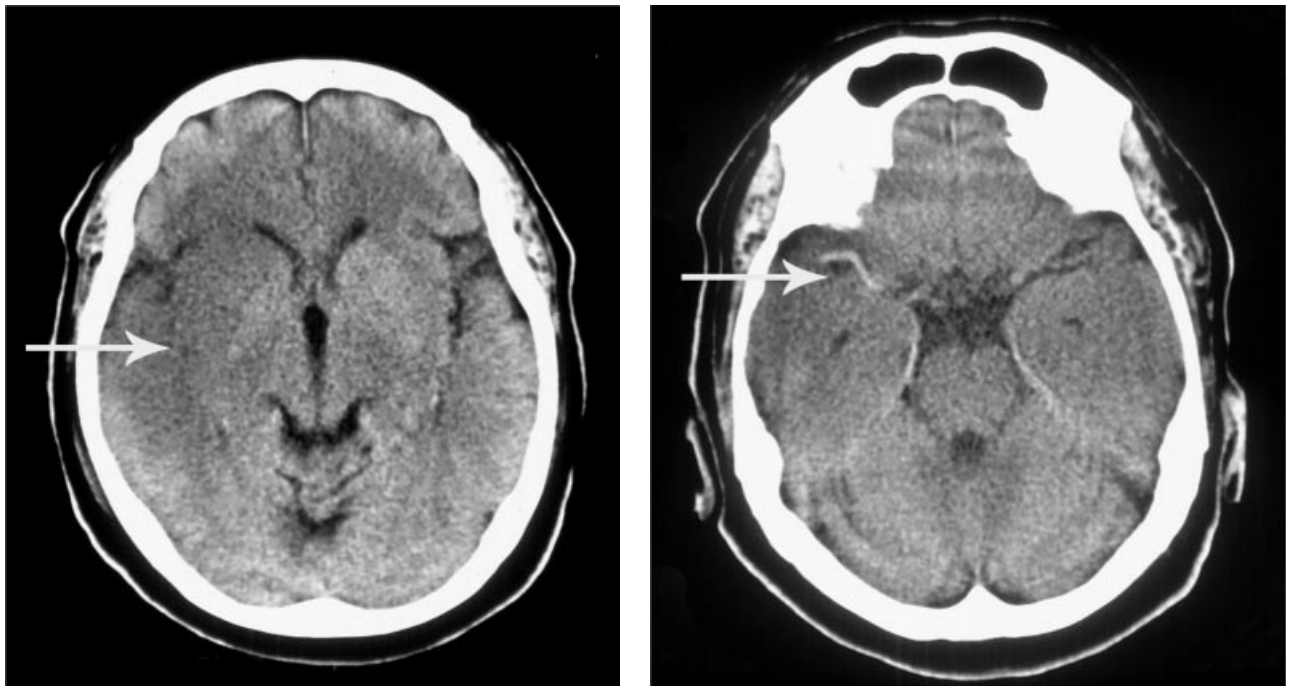
Initial investigations and imaging

The investigation of stroke and transient ischaemic attack are similar and are designed to establish the pathology, anatomy and mechanisms of symptoms and plan treatment. All patients should have urea, electrolytes, creatinine, full blood count, clotting screen, serum glucose and erythrocyte sedimentation rate carried out when they are first seen. A fasting glucose and fasting cholesterol should be done as soon as possible to exclude hypercholesterolaemia and diabetes. Electrocardiography will confirm the clinical assessment of heart rhythm or document evidence of ischaemia or acute myocardial infarction. If symptoms or clinical signs suggest respiratory involvement, such as heart failure or aspiration pneumonia, a chest X-ray should be added to these investigations. Further biochemical investigation of rarer causes of ischaemic stroke or stroke mimics will be directed by the clinical picture.

The immediate concern in acute stroke is the rapid differentiation of ischaemic from haemorrhagic stroke, which is most quickly and reliably demonstrated by non-contrast CT imaging. CT is sensitive and specific for haemorrhage within the first 8 days after stroke,[11] after which time reliability of detection decreases. MRI as an alternative is discussed below. All patients admitted with suspected stroke should undergo cranial imaging as soon as possible after admission and definitely within 24 h.[11,12] An immediate emergency scan is required for patients being considered for thrombolytic therapy or for those at risk of intracerebral haemorrhage by virtue of their presentation, including reduced conscious level, sudden onset of severe headache, a history of trauma, known coagulopathy or therapeutic anticoagulation.

Early signs of ischaemic stroke on CT include hyperdensity of a cerebral artery (showing thrombus *in situ*), slight hypodensity of the brain parenchyma leading to loss of the clear definition of the insular ribbon and lentiform nucleus, sulcal effacement reflecting tissue swelling and mass effect from more pronounced oedema (Figure 57.1).[13] A large hypodense area seen on CT reflects a poor prognosis and is sometimes used as a contraindication to thrombolysis because the risk of subsequent haemorrhage may be increased. This is because hypodensity reflects increased water content of the tissue and suggests both established infarction and the breakdown of the blood–brain barrier in this region. If the hypodensity is clearly delineated, this indicates that the infarction is well established and not hyperacute.

CT angiography (CTA) may be carried in the same session as non-contrast CT to visualize acute intracranial vessel



(a) (b)

Figure 57.1 (a) Early changes of right MCA territory infarction on CT scan. (b) MCA hyperdensity in the same patient.

occlusion, and also extravascular and intravascular stenosis or dissection. Acute CT perfusion imaging may also have a role in the future, allowing assessment of the extent of hypoperfusion in an arterial territory.

CT has the limitation that it is normal within the first few hours after onset in 30–40% of patients.[13] MRI is much better at detecting early changes of infarction and small infarcts, especially in the posterior fossa. MRI is also the technique of choice to identify haemorrhage if the scan is performed more than 8 days after onset. Several MRI sequences can be combined in one examination, termed 'multi-modal MRI', to produce a variety of clinically useful images. T_2 sequences provide good anatomical definition and show established infarction well, but are not very sensitive to early changes. Diffusion-weighted imaging (DWI) is much more sensitive than CT to the early and chronic changes of infarction. DWI becomes abnormal within a few minutes of onset of infarction and shows areas of restricted extracellular movement of water molecules, secondary to ischaemic membrane pump failure and cell swelling from excessive intracellular water, as bright areas. When the infarction is complete and cell lysis has occurred, usually between 7 and 14 days after onset, diffusion of water is facilitated and DWI will then show infarcts as dark areas. However, DWI may also show older infarcts as bright areas because of the phenomenon of 'T2 shine through'. The same MR sequences are therefore used to generate apparent diffusion coefficient (ADC) maps, which show acute infarction as dark and older infarcts as brighter areas.[14] Gradient echo imaging (GRE or T2*) is very sensitive to new and old haemorrhage. FLAIR imaging is highly sensitive to areas of gliosis secondary to established infarction and periventricular small-vessel disease (Figure 57.2). Magnetic resonance angiography (MRA) provides an alternative to CTA for vascular imaging. MR perfusion imaging can show areas of impaired blood flow secondary to arterial occlusion or severe stenosis.

Thus MRI has considerable advantages over CT, in addition to avoiding ionizing radiation. If available in the emergency situation, MRI with DWI can replace CT or may be used as an additional investigation. It should be considered a routine investigation in stroke patients in whom CT has failed to establish the diagnosis and is the investigation of choice after TIA. Limitations of MRI include patient tolerability, increased cost compared with CT and the requirement to exclude patients with metallic foreign bodies or implants.

In-hospital care

As with any acutely unwell patient presenting to hospital, the standard initial assessment and resuscitation of a patient with suspected stroke begin with attention to the airway, breathing and circulation.

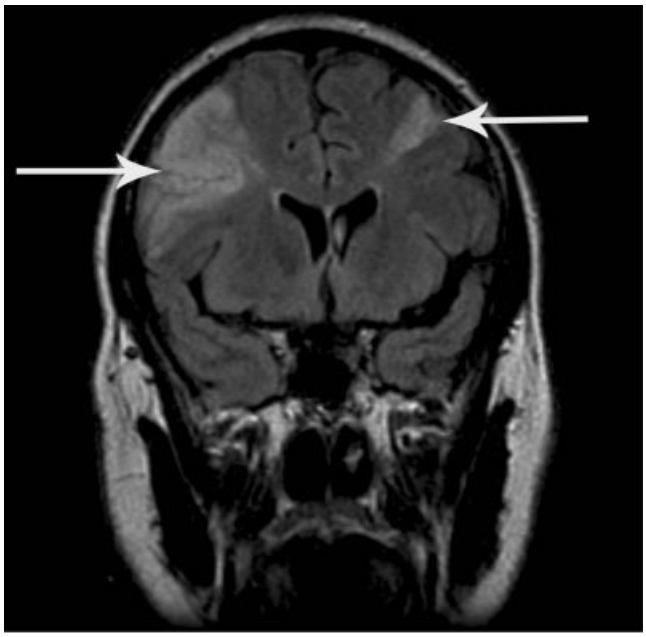


Figure 57.2 Multiple areas of cerebral infarction on FLAIR MR imaging.

Airway

The airway in a stroke patient may be obstructed secondary to a reduced level of consciousness or a buildup of secretions that cannot be effectively swallowed. Simple airway manoeuvres – for example, chin lift or jaw thrust – may be sufficient to clear the airway, or the use of an airway adjunct may be required. Patients with ongoing airway problems may warrant consideration of the involvement of an anaesthetist as an airway specialist.

Breathing

Effective breathing, and therefore effective oxygenation of the blood and brain, may be compromised by a number of mechanisms. A stroke affecting the respiratory centres of the brainstem may cause apnoea or bradypnoea. Problems with swallowing may precipitate aspiration pneumonia. In addition, hypoxaemia may arise through an associated condition such as heart failure or pulmonary embolism. Initial management is directed at treatment of the underlying cause, although guidelines recommend the application of inhaled oxygen only where a new desaturation below 92–95% exists on pulse oximetry.[12]

Circulation

In ascertaining the heart rhythm and blood pressure, some of the risk factors for stroke are being assessed. A finding of an elevated blood pressure is almost universal in patients within 48 h of stroke onset. This may occur either secondary to the stroke itself or reflect pre-existing hypertension. The management of high blood pressure in acute stroke is discussed later in this chapter.

Less common is the finding of hypotension. This may reflect severe dehydration, blood loss or cardiac failure and should lead to a search for the underlying cause, in addition to immediate treatment aimed at restoring the mean arterial blood pressure. The aim is to minimize secondary damage to the ischaemic penumbra in the brain and in the presence of a fixed intracranial pressure the cerebral perfusion pressure is dependent on the mean arterial blood pressure.

Blood sugar

Hypoglycaemia should be excluded – and treated if present – in all patients with neurological deficit, as it is an easily reversible cause of symptoms that mimic stroke. Hyperglycaemia following ischaemic infarction is associated with increase in infarct size and poor outcome. Raised blood glucose is a common finding at the time of presentation and severe hyperglycaemia is a contraindication to recombinant tissue plasminogen (rt-PA) administration. However, the benefit of early correction of blood glucose in stroke patients at the time of presentation remains uncertain. Preliminary investigation of the effects of 'tight' control of blood sugar levels in a stroke patient population has highlighted the high incidence of unintended hypoglycaemia as a consequence,[15] a factor which may offset any potential benefit of the treatment. Control may be achieved by the administration of an insulin infusion or by the administration of subcutaneous insulin, but close monitoring of blood glucose is mandated. It has been suggested that non-diabetic patients receive less intensive correction of blood glucose levels, since hyperglycaemia at the time of presentation may not reflect underlying insulin deficiency or resistance and may be a transient state with a return to baseline levels.[15]

Environment

Fever, defined as a core temperature of $>37.5^{\circ}C$, should prompt a search for a source, as fever carries increased mortality and worse neurological outcome and may indicate an underlying aetiology for the stroke, such as endocarditis. Lower respiratory tract infection and urinary tract infection are common complications of stroke. Antibiotic prescription should be considered, but the effect on clinical outcome of active lowering of the temperature with antipyretics is not clear.

Early attention should also be paid to nutrition and hydration. For those patients in whom a swallowing disorder is suspected, it is appropriate to provide nutrition via a

nasogastric tube and request a formal specialist assessment of swallowing. Regardless of the mode of administration of nutrition, normal hydration should be maintained.[12]

Thrombolysis and recanalization

The introduction of intravenous alteplase (an rt-PA) as treatment for acute ischaemic stroke has transformed stroke care. However, its benefits in acute stroke are tempered by the risk of precipitating intracranial haemorrhage and the strict licensing conditions that govern its safe use. The NINDS (National Institute of Neurological Disorders and Stroke) rt-PA Stroke Study[16] included patients under the age of 80 years with a carotid arterial or vertebrobasilar arterial distribution stroke, not in coma, who could start treatment within a 3 h time window and randomized patients to receive either intravenous thrombolysis with alteplase or placebo. Impairment was measured using the NIH Stroke Score. Intracranial haemorrhage occurred in 6.4% of thrombolysed patients within the first 36 h, compared with 0.6% of those randomized to placebo. However, patients treated with t-PA were around 30% more likely to have minimal or no disability at 3 months.[16] Pooled analysis of the NINDS trial with several other trials of thrombolytic therapy confirmed that, when given within 3 h, intravenous thrombolysis significantly reduces the risk of death or dependency, with a linear relationship between time from stroke onset to treatment and degree of benefit, perhaps extending beyond 3 h.[17] The ECASS-3 trial subsequently confirmed that intravenous alteplase can be given safely to patients under the age of 80 years between 3 and 4.5 h after onset, with a small overall benefit.[18]

Contraindications to thrombolysis include the presence of intracranial haemorrhage, seizure at the time of onset of neurological deficit, recent major surgery or major trauma, severe hypoglycaemia or hyperglycaemia, pancreatitis or pericarditis, recent gastrointestinal or urinary tract bleeding, concurrent anticoagulation with raised INR, severe thrombocytopenia and recent myocardial infarction (Table 57.5). Very severe, mild deficit or rapidly resolving symptoms may also be contraindications. Hypertension, with blood pressure >180/110 mmHg, should be treated cautiously before the administration of thrombolytics. Aspirin is contraindicated within the first 24 h after t-PA administration because of an increased risk of death.[19] If intracranial haemorrhage should result, management guidelines vary, but the discontinuation of ongoing infusion of thrombolytic agent is mandatory. Blood samples should be analysed to provide an up-to-date clotting profile and consideration should be given to the administration of reversal agents (for example, cryoprecipitate). In the event of a severe haemorrhage, neurosurgical consultation may be necessary.

Table 57.5 Contraindications to thrombolysis with tPA.

1	Symptoms only minor or rapidly improving
2	Haemorrhage on pretreatment CT (or MRI)
3	Visible changes pretreatment CT (or MRI) of infarction >one-third of MCA territory
4	Suspected subarachnoid haemorrhage
5	Active bleeding from any site
6	Recent gastrointestinal or urinary tract haemorrhage within 21 days
7	Platelet count less than $100 \times 10^9\ l^{-1}$
8	Recent treatment with heparin and APTT above normal
9	Recent treatment with warfarin and INR elevated
10	Recent major surgery or trauma within the previous 14 days
11	Recent post-myocardial infarction pericarditis
12	Neurosurgery, serious head trauma or previous stroke within 3 months
13	History of intracranial haemorrhage (ever)
14	Known arteriovenous malformation or aneurysm
15	Recent arterial puncture at non-compressible site
16	Recent lumbar puncture
17	Blood pressure consistently above 185 mmHg systolic or 110 mmHg diastolic
18	Abnormal blood glucose (<3 or >20 mmol l^{-1})
19	Suspected or known pregnancy
20	Active pancreatitis
21	Epileptic seizure at stroke onset

Source: adapted from the NINDS protocol.[16]

The ongoing Third International Stroke Trial (IST-3) seeks to determine whether thrombolysis provides benefit up to 6 h from the onset of symptoms and the effectiveness of this therapy in patients over the age of 80 years, who were not included in previous trials.

Providing access to thrombolysis for stroke requires the provision of hyperacute stroke units (HASUs) and well-developed pathways organized to deliver urgent access to brain imaging and stroke expertise, with the aim of achieving door-to-needle time from arrival of the patient to the start of alteplase infusion of less than 30 min, with facilities to monitor patients appropriately following administration of alteplase.

Newer modalities of treatment, such as endovascular mechanical dissolution of thrombus, intra-arterial thrombolysis and acute angioplasty to recanalize an occluded vessel, continue to undergo evaluation and are not yet part of the routine treatment of acute stroke. These treatments require the involvement of an interventional neuroradiology service.

Neuroprotective drugs

The ischaemic penumbra, an under-perfused area of brain surrounding an area of infarcted tissue which is potentially salvageable, offers a target for therapeutic intervention.[20] In

general, it is thought that the higher the residual perfusion of an area, the longer ischaemia may be tolerated before leading to cessation of neuronal electrical activity, failure of ion homeostasis and cell death. In addition to thrombolysis to restore perfusion of this area, a number of 'neuroprotective' agents have been trialled, with disappointing results. Biochemically or physiologically logical treatments, for example using calcium channel inhibitors to reduce vasogenic oedema, have not translated into a clinical improvement. Included in the definition of neuroprotection is therapeutic hypothermia, which remains an experimental procedure. However, tight control of physiological parameters as described above, for example, prevention of hypoxia, is likely to have an important role in limiting secondary damage after ischaemia.

Neurosurgery for ischaemic stroke

Neurosurgical intervention in ischaemic stroke is generally considered in two circumstances. In large middle cerebral artery territory infarction, cerebral oedema develops over the immediate days following the event as brain cells swell, and lyse and may result in midline shift and increased intracranial pressure, sometimes referred to as *'malignant MCA infarction'*. Should cerebral oedema be severe, transtentorial herniation may result in death from brainstem compression. Neurosurgery in patients at imminent risk of brain herniation consists of a duraplasty and the formation of a large bone flap to allow room for swelling of the cranial contents.

A pooled analysis of three randomized controlled trials of craniectomy for malignant MCA infarction (DECIMAL, DESTINY and HAMLET)[21] showed a significantly improved outcome, as measured by the Modified Rankin Scale (mRS), which records disability and death on a scale of 0–6 (where 0 is no symptoms and 6 is death), in the surgical groups versus standard medical treatment. Neuroimaging criteria used in the trials differed, but all aimed to quantify the volume of brain tissue involved as either an absolute volume ($>145\,cm^3$) or a relative volume (more than two-thirds of the MCA territory). These are patients with a poor prognosis and mortality in this group is high. The primary endpoint of the analysis was death or disability. The absolute risk reduction of a bad outcome (mRS $\leq$4) in the surgical group versus the control group was 51% (95% CI, 34–69%) and more patients survived in the surgical group (78% versus 29%).[21] The authors concluded that this represented a number-needed-to-treat (NNT) of 2 for both mRS $\leq$4 and to prevent one death. Only patients younger than 60 years benefited from decompression, with patients over the age of 50 years suffering a higher rate of death or severe disability after surgery compared with those aged under 50 years.

Posterior fossa infarction may also warrant consideration of neurosurgery. The volume of the posterior fossa is small compared with that of the rest of the cranium and oedema secondary to a large cerebellar infarct is tolerated poorly, with the potential for brainstem compression and obstruction of the fourth ventricle and resultant hydrocephalus.

Palliative care

Unfortunately, there are patients who suffer a stroke that is so extensive that they will not recover. In these circumstances, treatment is directed at the relief of pain or other distressing symptoms such as restlessness, mood disturbance or confusion. For those who survive the first few days, spasticity, pressure areas and incontinence, among other neurological consequences, may need specific attention. An open discussion with family members about prognosis and continuing communication is essential. Good communication with ward staff and clear documentation in the notes may prevent unnecessary investigation or intervention. Involvement of local inpatient palliative care services may be beneficial, but there is relatively little published research or guidance in this area.

Stroke units

Care of the patient with stroke has been revolutionized with the introduction of specialized stroke units, which seek to standardize management and coordinate a multidisciplinary team of experts. Features of stroke unit care include early mobilization, medical, nursing and allied professional staff specialized in stroke care and specific investigation such as assessment of swallowing.[22] In a stroke unit, there should also be regular monitoring of physiological variables such as oxygen saturation, blood pressure and temperature. It is unknown exactly which of these interventions is most responsible for an improvement in outcome and there are additional unmeasurable factors, such as the professional dedication and continuing education of ward staff, that may also contribute. There is also specific attention given to the modification of risk factors for recurrent stroke, such as blood pressure management and antithrombotic therapy. However, it is clear that the majority of benefit relates to early intervention and therefore current NICE guidelines in the UK recommend that all stroke patients should be admitted without delay directly to an acute stroke unit.[12]

Systematic review of smaller stroke unit studies in 1997 suggested an overall benefit for stroke unit care and paved the way for the widespread implementation of stroke units. At the conclusion of follow-up, the combined odds ratio of death in a stroke unit versus conventional care was 0.82 (95% CI, 0.69–0.98). The odds ratio of death or dependency was 0.71 (95% CI, 0.61–0.84).[22] There was no

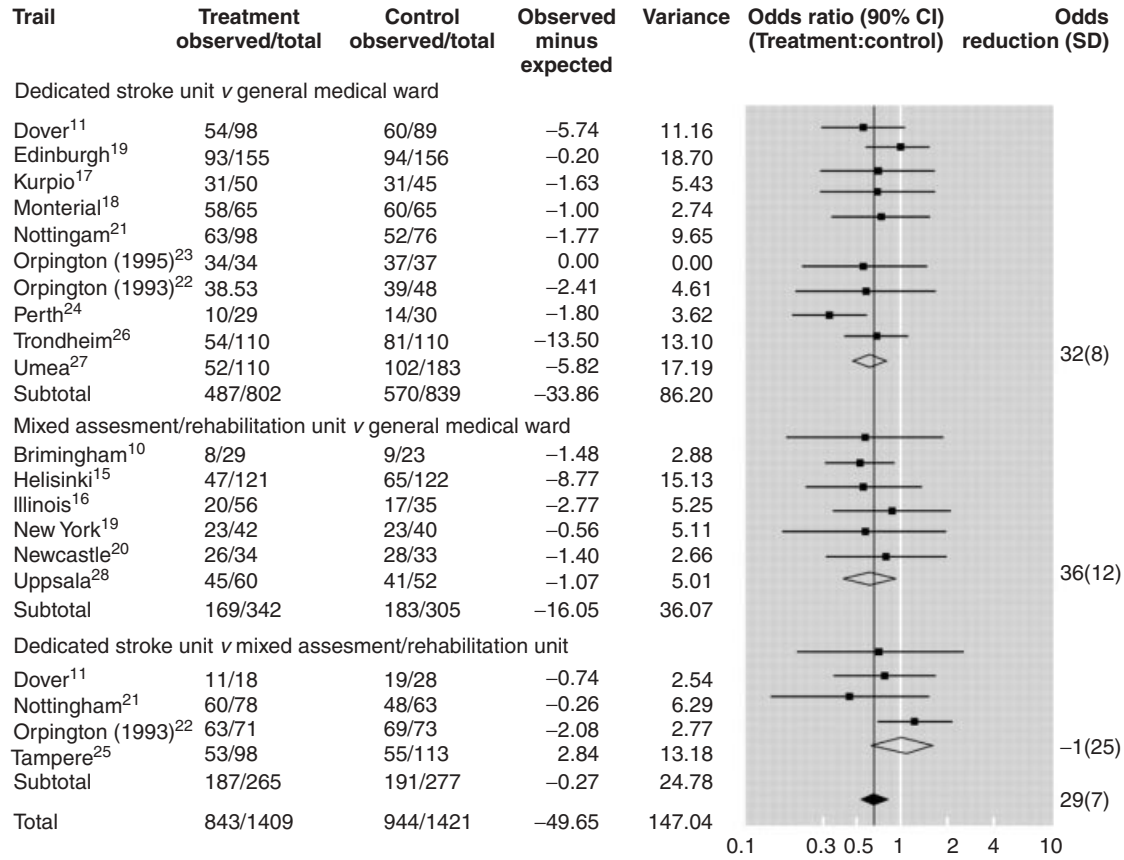


Figure 57.3 Systematic review of randomised trials of organized inpatient care after stroke: odds ratio (95% confidence interval) of death or requiring institutional care at the end of scheduled follow-up in patients receiving stroke unit compared with conventional care. Please note that references given in this figure relate to citations in the original article. Reproduced from The Stroke Unit Trialists' Collaboration (1997),[22] with permission from BMJ Publishing Group Ltd.

statistically significant difference in the calculated length of stay of patients in either group and subgroup analysis did not reveal a difference in groups of different gender, age or stroke severity, leading to the conclusion that stroke unit care is effective and that it should be offered to all stroke patients regardless of individual characteristics (Figure 57.3). Subsequent updated reviews have found similar results.

Secondary prevention

Patients who present with minor stroke or TIA have a high risk of early recurrence. Without treatment, as many as 10% of patients may experience a further event. Certain clinical features predict a high early risk and a number of scores have been developed to predict those at highest risk. The ABCD2 score is the one most commonly used in the UK[23] (Table 57.6). Patients with ABCD2 score of ≥4 should undergo further investigations and initiation of secondary prevention measures should be organized within 24 h of onset. Rapid access clinics are therefore an essential component of a comprehensive stroke service.

Antiplatelet therapy

The benefit of early aspirin administration, after exclusion of haemorrhagic stroke, was demonstrated by the International Stroke Trial (IST).[24] This study compared aspirin with subcutaneous heparin and therapy combining both aspirin and heparin, given within 48 h of onset in 19 435 patients, with a control group receiving neither aspirin nor heparin. In the analysis of aspirin versus no-aspirin groups, those patients allocated aspirin experienced a significantly lower risk of recurrent stroke at 14 days than patients not allocated aspirin (2.8% versus 3.9%).[24] There is therefore a small but significant benefit to early treatment with aspirin, a low-cost intervention. Typically, an initial dose of 300 mg is given, followed by the initiation of long-term therapy with 75 mg daily.

Subsequent work has aimed to identify whether the addition of further therapy, in the form of dipyridamole

Table 57.6 ABCD2 score.[23]

Feature		ABCD2 score
Age	≥60 years	1
	<60 years	0
Blood pressure	SBP >140 or DBP >90 mmHg	1
	SBP <140 and DBP <90 mmHg	0
Clinical features	Unilateral weakness	2
	Speech disturbed without weakness	1
	Others	0
Duration	≥60 min	2
	10–59 min	1
	<10 min	0
Diabetes	Diabetic	1
	Not known to be diabetic	0
Total		Range 0–7

Table 57.7 NICE guidelines for early management and investigation of TIA.[12]

- Start daily aspirin (300 mg) immediately
- Introduce measures for secondary prevention as soon as the diagnosis is confirmed, including discussion of individual risk factors
- Specialist assessment within 24 h of onset, including decision on brain imaging, for patients at high risk of stroke (ABCD2 score of ≥4 crescendo TIA)
- Specialist assessment within 1 week of symptom onset, including decision on brain imaging, for patients at lower risk of stroke (ABCD2 score of ≤3 or presenting more than 1 week after symptoms have resolved)
- Use diffusion-weighted MRI for brain imaging, except where contraindicated. For these people, use CT scanning
- If the person is identified as a candidate for carotid endarterectomy on specialist assessment, perform carotid imaging within 1 week of symptom onset
- Make sure that carotid imaging reports state clearly which criteria (ECST or NASCET) were used when measuring the extent of carotid stenosis

or clopidogrel, offers any increased benefit in longer term secondary prevention after ischaemic stroke or TIA. Aspirin combined with modified-release dipyridamole in the ESPRIT study produced an absolute risk reduction of 1% (95% CI, 0.1–1.8%) compared with aspirin alone for the primary outcome of death from stroke, myocardial infarction or other vascular conditions, without an increase in the risk of haemorrhage.[25] The risk ratio for the primary outcome was similar when the trial results were compared with previous studies in a meta-analysis. At higher doses given acutely, dipyridamole exhibits vasodilatory properties and therefore caution is advised in patients who are known to have a coronary arterial disease. The principal side effect limiting the tolerability of dipyridamole is headache.

Clopidogrel has also been investigated as an alternative to the combination of aspirin and dipyridamole. The PRoFESS Study[26] reported a similar rate of recurrent stroke in patients randomized to treatment with clopidogrel or treatment with aspirin and extended-release dipyridamole, with similar rates of major haemorrhage. A previous study had demonstrated an increased risk of bleeding with the combination of clopidogrel and aspirin in long-term use compared with clopidogrel alone, hence the use of clopidogrel monotherapy in the PRoFESS Study.[27] Therefore, clopidogrel as monotherapy provides an alternative to the combination of aspirin and dipyridamole for secondary prevention of stroke and is the antiplatelet of choice for patients who cannot tolerate aspirin or dipyridamole in combination.

Secondary prevention after stroke requires appropriate management of vascular risk factors and treatment focused on identification of the likely cause of the TIA or stroke. Thorough investigation of patients presenting as stroke or TIA is an important component of secondary prevention measures (Table 57.7).

Blood pressure management

There is good evidence that lowering blood pressure reduces the risk of recurrent stroke, whatever the initial level of blood pressure. Secondary prevention with an antihypertensive drug is typically initiated 7–14 days after stroke onset, when any acute, transient, blood pressure elevation will have settled. The benefits and risks of acute blood pressure lowering in the hypertensive patient presenting acutely with stroke are less certain. Lowering of blood pressure levels initially within the normal range, and also good control of hypertension, with the combination of a diuretic and an angiotensin-converting enzyme (ACE) inhibitor drug, reduced the long-term risk of recurrent stroke by 40% in the PROGRESS trial.[28] An ACE inhibitor alone is not nearly as effective, probably because the benefit depends on how far blood pressure is lowered.

Physiological changes in the cerebral circulation occur at the time of stroke and cerebral autoregulation may be impaired. In an acute stroke, lowering mean arterial blood pressure may reduce the cerebral perfusion pressure and, in areas with critically reduced blood flow (the ischaemic penumbra), this may lead to infarction. However, in patients with evidence of cardiac dysfunction or acute myocardial infarction, the balance of risks may be altered to favour hypotensive therapy. Severe hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >105 mmHg) is a contraindication to thrombolytic therapy. If blood pressure is therapeutically lowered in acute stroke,

reductions in blood pressure should be closely monitored and rapid falls avoided.

Cholesterol management

The finding of an elevated fasting cholesterol level should prompt the involvement of a dietician or nutritionist.There is good evidence that lowering serum cholesterol levels of $>3.5 mmol l^{-1}$ with, for example, simvastatin 40 mg nocte results in a substantial reduction in the long-term risk of recurrent stroke and myocardial infarction of about one-third.[29,30]

Diabetes management

Management of prolonged fasting hyperglycaemia is in accordance with guidelines for the standard management of diabetes. The evidence suggests that tight control of blood sugar levels over the long term in diabetes has more of an effect on reducing rates of myocardial infarction than stroke rates, whereas the opposite is the case for hypertension. The blood pressure readings in diabetic patients during follow-up after stroke should therefore be maintained at or below the target of 130/80 mmHg.

Anticoagulation

In acute stroke, unfractionated heparin, given subcutaneously, reduces the rate of recurrent stroke and pulmonary embolism, but at the expense of an increase in cerebral haemorrhage of similar magnitude that offsets potential benefit.[24] There is also a significant increase in extracranial bleeding. Low molecular weight heparin (LMWH) has similarly failed to demonstrate a therapeutic benefit at treatment dose. The balance of evidence, therefore, does not favour heparin use in acute stroke. Anticoagulation is therefore reserved for the patient with atrial fibrillation at risk of stroke or for those in whom another indication exists (e.g. prosthetic heart valve or pulmonary embolism).

The only situation where anticoagulation with warfarin has been found to be more effective than antiplatelet therapy is in the prevention of stroke recurrence after TIA or ischaemic stroke associated with atrial fibrillation. Randomized trials have shown that any benefit in the first 2 weeks after onset of stroke is offset by an increase in cerebral haemorrhage. Initiation of warfarin should therefore be delayed until after 2 weeks, except after TIA and minor stroke, when it is logical to start immediately. Warfarin reduces the risk of recurrent stroke in suitable patients with atrial fibrillation by about 70%.[31] Aspirin and other antiplatelet agents are much less effective in preventing recurrent stroke in patients with atrial fibrillation, but provide an alternative for those who cannot or will not take warfarin. There is an assumption that has not been tested in randomized trials that other causes of cardioembolic stroke will also benefit from anticoagulation, including patients with recent myocardial infarction, congestive valvular heart disease and cardiomyopathies. Safe anticoagulation will require patient participation, monitoring and adjustment of therapy and an acceptably low risk of falls.

Carotid artery stenosis

Carotid artery stenosis is responsible for 20–30% of cases of anterior circulation ischaemic stroke and TIA and between 5 and 10% will need endarterectomy (or stenting) to prevent recurrence. The arterial narrowing is usually caused by atherosclerosis, which becomes more prevalent with age and is accelerated by risk factors. Dissection is an important cause in younger patients.

Atherosclerosis

Atherosclerosis is the commonest arterial disorder in developed countries and, when complicated by thrombosis and embolism, may result in ischaemic stroke, myocardial infarction and also peripheral arterial disease. The process of atheroma formation occurs over many years, beginning with low-density lipoprotein (LDL) cholesterol moving into the subendothelium, often at sites of endothelial injury or haemodynamic stress. In the cerebral circulation this occurs at sites of arterial branching, especially the bifurcation of the common carotid artery into the internal carotid artery (ICA) and external carotid artery (ECA). The LDL is oxidized by macrophages and smooth muscle cells. Production of growth factors and cytokines attracting more immune cells, foam cell accumulation and smooth muscle proliferation all result in the growth of an atherosclerotic plaque.[32] Risk factors that accelerate the formation of atherosclerosis include cigarette smoking, diabetes mellitus, age, dyslipidaemia and hypertension. Genetic predisposition may also play a role.

Plaques with a fatty core and a fibrous cap then spread along and around the arterial wall, encroaching on the media and ultimately leading to narrowing of the vessel lumen and stiffening of the arterial wall. A defect in the fibrous cap, due to rupture or erosion, predisposes to thrombosis at that site. Platelets adhere to the vessel wall and are activated, initiating blood coagulation. This is the site of action for antiplatelet agents used in the secondary prevention of stroke. Thrombosis may initially be incorporated into the plaque, but as the plaque grows, the lumen of the vessel may become obstructed, causing a narrowing or stenosis. The atherothrombotic plaque may completely occlude the artery or embolization from the plaque may cause either transient or permanent obstruction of a smaller distal artery, resulting in cerebral or ocular symptoms. Most strokes and TIAs secondary to carotid stenosis occur as a result of

thromboembolism. Hypoperfusion of arterial territories is a relatively rare cause of symptoms compared with other sites, because of collateral supply via the circle of Willis.

Arterial dissection

A rare cause of carotid artery stenosis in the elderly population, dissection may be spontaneous, traumatic or associated with underlying connective tissue disease (such as Marfan syndrome or Ehlers–Danlos syndrome). Most commonly, dissection occurs following minor neck or head trauma associated with sudden rotation of the neck. The ICA is torn against the second cervical vertebra and a haematoma forms in the arterial wall, which can narrow the vessel lumen, leading to thrombosis. Alternatively, an intimal free flap may promote thromboembolism. There may be a delay of up to several days between the event and symptoms in the territory of the anterior cerebral circulation. Diagnostic clues suggesting dissection include a Horner syndrome resulting from compression or ischaemia of the sympathetic chain which surrounds the carotid artery in the neck. Cross-sectional MRI with fat-suppressed sequences is the investigation of choice, revealing a characteristic crescent-shaped haematoma in the carotid arterial wall (Figure 57.4).

Subsequent management is controversial, with most centres anticoagulating patients with heparin and subsequently warfarin, but there is no good evidence of benefit in preventing recurrent stroke compared with aspirin. Stenting may be an option for some patients resistant to medical treatment.

Investigations

Carotid artery atheroma may be found after investigating a neurological event, be sought on imaging after clinical examination reveals a carotid bruit or may be an incidental finding during preoperative workup for procedures such as cardiac bypass surgery. Auscultation for carotid bruit, however, is not a reliable screening test for significant carotid stenosis. A localized bruit is indeed usually caused by a narrowing of the artery, but the extent and significance of the stenosis cannot be predicted by the presence of a bruit. A very tight stenosis, for example, may not cause a bruit or an ECA stenosis of little clinical significance may cause a loud bruit.

The level where the carotid artery divides into ICA and ECA branches varies, but in most patients it is possible to examine the common carotid artery, bifurcation and proximal portions of the ICA and ECA with ultrasound. B-mode duplex ultrasound with Doppler measurement of flow velocities in these arteries is therefore commonly used to screen for ICA stenosis. Although the artery itself may be visualized using plain ultrasound, estimation of the degree of stenosis with accuracy is difficult. Indirect evidence is therefore gathered through measurement of the velocity of flow in the longitudinal direction.[33] As the systolic pulse passes a stenosis, the velocity of blood will tend to increase and it is the absolute velocity of flow both distal to the stenosis and prior to the stenosis that are assessed (Table 57.8). Grading of stenosis for a given examination varies according to the method used. It is important to note which method is being applied.

Table 57.8 Derived figures for Doppler ultrasound criteria for grading ICA diameter reduction.[33]

Diameter reduction (%)	Peak systolic velocity ($cm\ s^{-1}$)	End diastolic velocity ($cm\ s^{-1}$)	PSV_{ICA}/PSV_{CCA}[a]
0–29	<100	<40	<3.2
30–49	110–130	<40	<3.2
50–59	>130	<40	<3.2
60–69	>130	40–110	3.2–4.0
70–79	>230	110–140	>4.0
80–95	>230	>140	>4.0
96–99		'String flow'	
100		'No flow'	

[a]ICA = internal carotid artery; CCA = common carotid artery, PSV_{ICA}/PSV_{CCA} = ratio of the velocities.

It is also possible to derive measurement of the intimal–medial thickness of the carotid artery from B-mode ultrasound, which can be used to measure plaque thickness or progress and to visualize portions of the vertebral arteries in some subjects, but the clinical utility of the latter is limited by the superiority of other contrast methods.[33]

Ultrasound is a safe, non-invasive and relatively inexpensive technique, but its utility remains limited by the requirement of a high degree of operator skill. Results are subject to interobserver variation and technical limitations of the procedure include acoustic shadowing caused by calcified plaque and difficulty in studying a tortuous vessel where flow velocities may appear increased.[33]

Because of these limitations, most units confirm abnormal findings on ultrasound with a second non-invasive imaging modality before considering surgery or stenting for carotid stenosis. Catheter angiography may be required if the non-invasive investigations are discordant or difficult to interpret.

MRA, with or without intravenous contrast, was the first alternative non-invasive technique used for the investigation of arterial pathology in the neck and head to confirm the presence of carotid artery stenosis (Figure 57.5) in patients who have undergone preliminary ultrasound investigation, but MRA may also be used as a screening investigation. The limitations of MRA include patient tolerability and

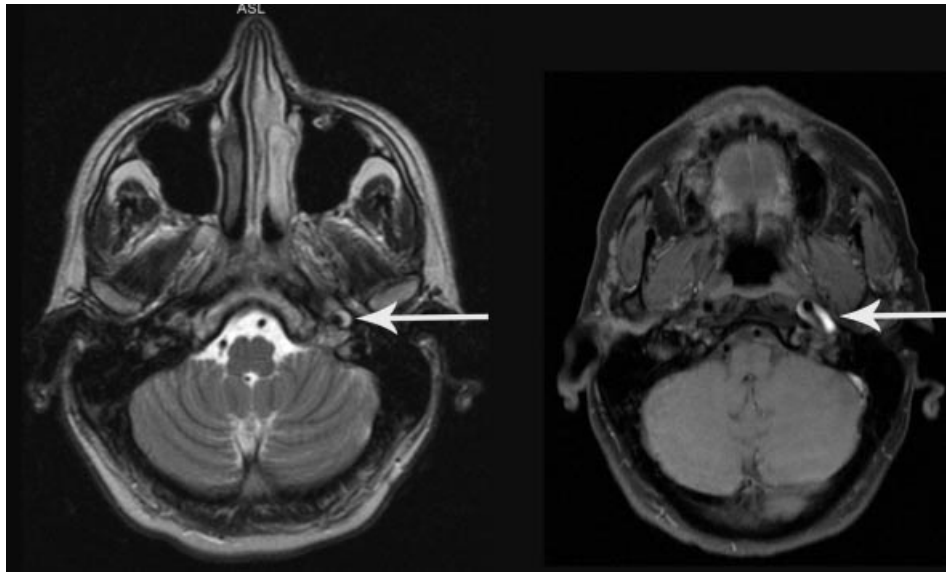


Figure 57.4 Carotid artery dissection on MR imaging – there is left carotid dissection from the high cervical to at least the laceral segment.

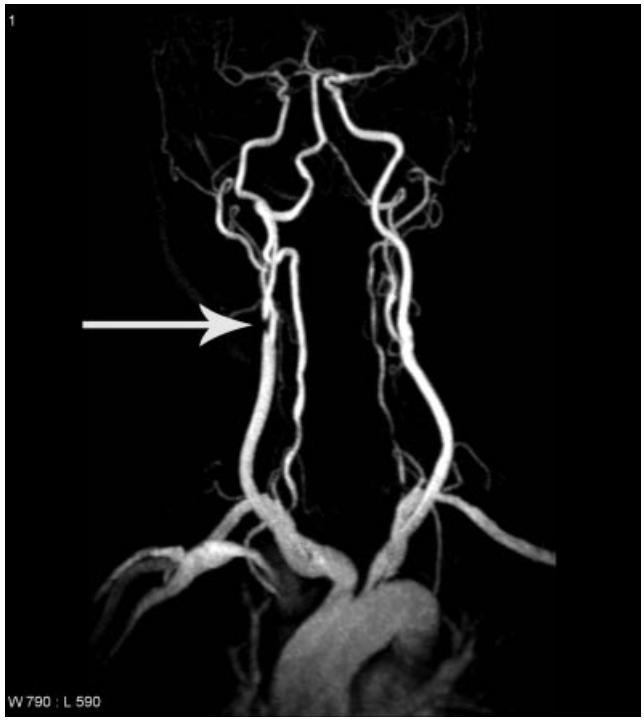


Figure 57.5 Carotid artery stenosis.

safety with metallic implants. Technical limitations include misinterpretation of swallowing artefact or turbulent flow as stenosis. MRA and/or duplex ultrasound are increasingly being replaced by CTA with intravenous contrast because it is often combined with CT in the initial evaluation of stroke.

The limitations of CTA include contrast toxicity (including renal impairment), contrast allergy and poor visualization of stenosis if there is heavy plaque calcification.

Catheter angiography is the 'gold standard' investigation for carotid artery stenosis, but this procedure carries with it a significant risk of stroke or TIA of between 0.5 and 2%, depending on indications. The catheter may dislodge atheromatous plaque, dissect the arterial wall or thrombus may form on the catheter. The intravenous contrast administered carries the same risks as for other indications, namely headache, nausea, bradycardia and renal failure. For these reasons, angiography is normally preceded by non-invasive investigation and should only be performed in experienced neurovascular units.

Carotid endarterectomy

The case for intervention

To warrant intervention, the risk of stroke that accompanies carotid endarterectomy (CEA) must be less than the natural risk of stroke in the patient receiving best medical management, and the benefit of surgery must be sufficient to justify the costs to healthcare providers and risks to the patient.

Symptomatic patients

Large randomized clinical trials have demonstrated a benefit of CEA for severe symptomatic carotid artery stenosis compared with medical treatment alone. In the European Carotid Surgery Trial (ECST),[34] over 3000 patients with any degree of carotid stenosis who had a TIA or minor stroke in the 6 months prior to randomization were

randomized to receive CEA or best medical management alone. Concurrently, the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[35] randomized over 2800 patients with >30% carotid stenosis who had symptoms within 3 months of randomization to CEA or best medical management. A meta-analysis of these trials indicates a clear advantage of CEA over medical management for the patients with more severe stenosis, provided that the perioperative risk of stroke or death is no more than 5%.[36] NICE guidelines for the management of carotid stenosis are given in Table 57.9.

ECST and NASCET used different denominators to measure the severity of stenosis, but the NASCET method in which the diameter of the stenosis is compared with the diameter of the distal ICA has become the standard method. The absolute risk reduction of ipsilateral ischaemic stroke or death in those patients with 70–99% NASCET stenosis undergoing CEA was 16% ($p < 0.001$)[36] (Figure 57.6). Patients with 50–69% NASCET stenosis also achieved a risk reduction, but the margin of benefit was slimmer. Below this stenosis threshold, there was evidence of overall harm. In subgroup analyses, male gender, advancing age and recent symptoms were identified as factors conferring additional benefit to the procedure.

Table 57.9 NICE guidelines for the management of carotid stenosis.[12]

- All people with suspected non-disabling stroke or TIA who after specialist assessment are considered as candidates for carotid endarterectomy should have carotid imaging within 1 week of onset of symptoms
- People who present more than 1 week after their last symptom of TIA has resolved should be managed using the lower risk pathway
- People with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of 50–99% according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria or 70–99% according to the ECST (European Carotid Surgery Trialists' Collaborative Group) criteria should:
  - be assessed and referred for carotid endarterectomy within 1 week of onset of stroke or TIA symptoms
  - undergo surgery within a maximum of 2 weeks of onset of stroke or TIA symptoms
  - receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice)
- People with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of <50% according to the NASCET criteria or <70% according to the ECST criteria should:
  - not undergo surgery
  - receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice)
- Carotid imaging reports should clearly state which criteria (ECST or NASCET) were used when measuring the extent of carotid stenosis

Asymptomatic patients

The benefits of surgery for asymptomatic carotid stenosis and symptomatic stenosis with more than 6 months since last symptoms are less clear-cut than for symptomatic stenosis. Two large randomized controlled trials have addressed this issue.[37,38]

In the Asymptomatic Carotid Atherosclerosis Study (ACAS), over 1600 patients with asymptomatic carotid stenosis of 60% or more were randomized to receive CEA or best medical treatment. The results showed that surgery significantly reduced the overall 5 year risk of ipsilateral stroke or any perioperative stroke or death from 11 to 5.1% ($p = 0.004$), but not the risk of major stroke. The complication rate in the surgical arm approached 3% at 30 days when preoperative angiography was included in the analysis.[37]

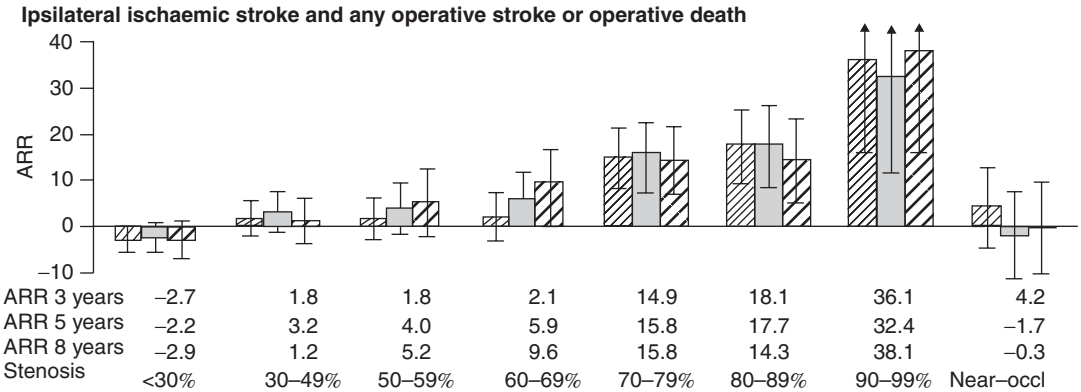


Figure 57.6 Effect of surgery on absolute risk of main trial outcomes at 3, 5 and 8 years' follow-up by degree of symptomatic carotid stenosis, in analysis of pooled data from ECST and NASCET. Reprinted from Rothwell *et al.* (2003),[36] Copyright 2003, with permission from Elsevier.

The Asymptomatic Carotid Surgery Trial (ASCT) randomized over 3000 patients to a policy of immediate or deferred carotid endarterectomy (until surgery seemed to be more clearly indicated, for example in the presence of related symptoms), for asymptomatic 60–99% stenosis. The results showed a benefit to immediate surgery in terms of reducing the 5 year risk of all strokes and perioperative death from 11.8 to 6.4% ($p < 0.0001$). However, subgroup analysis showed no evidence of benefit in patients older than 75 years or in women after taking into account the risks of surgery. There was a less marked benefit in terms of reducing the risk of fatal or disabling stroke. The 30 day rates of stroke or death after CEA in both trials were similar at around 3%.[38]

The results from these trials suggest that although surgery for asymptomatic surgery may be less risky than in symptomatic disease, the benefits of reducing the risk of major stroke or death are less certain. In particular, the rate of stroke in patients with asymptomatic carotid stenosis treated medically in the trials was very low at around only 2% per annum and in order to provide a net benefit with surgery an experienced surgeon working in a centre with low complication rates was necessary. The trials were conducted several years ago at a time when statins were not in widespread use, blood pressure was less well controlled and dual antiplatelet therapy was not used routinely. It is therefore likely that with better medical management, the rates of ipsilateral stroke associated with asymptomatic carotid stenosis will be even lower than recorded in the trials, which could negate any potential benefit of surgery.

These results together suggest that patients with asymptomatic stenosis aged over 75 years or those with less than 60% stenosis should not be offered surgery. Those who otherwise meet inclusion criteria may be offered surgery, but in the knowledge that their risk of stroke with best medical treatment is low. If patients and their neurologists and surgeons opt for medical management, then they should be educated about the symptoms of TIA and stroke and urged to present to a doctor should these occur.

Carotid artery stenting

Carotid artery stenting has developed as an alternative to the more established procedure of CEA. In theory, there are several potential benefits to the patient of this approach. This procedure is normally carried out under local anaesthesia, avoiding the risks of a general anaesthetic. Patients may recover faster from a procedure performed under local anaesthesia, thereby reducing the length of hospital stay. The other major advantage of an endovascular approach is that there is no need for an incision in the neck and the incidence of haematoma, infection and cutaneous or cranial nerve injury is reduced. Complications at the site of endovascular access in the groin are rare.

However, there are few interventionists with extensive experience of angioplasty and stenting in the carotid artery, although experience with endovascular surgery elsewhere in the body is increasing. Endovascular treatment of carotid stenosis may lead to distal embolization of thrombus to the brain during the passage of the catheter through a tight stenosis, and simple balloon angioplasty has been replaced with stenting and the use of cerebral protection devices (either filters or occlusion devices) to try to mitigate this problem. Stents are thought to cause less arterial dissection than balloon angioplasty, but transcranial Doppler studies have shown that embolization frequently occurs during deployment of the stent and during post-stent dilation. The utility of cerebral protection devices is debated and research in this area has not always shown an improved outcome with the use of a protection device.

Although the recovery time following successful endovascular intervention is short, the cost benefits of a reduced length of inpatient stay may be overshadowed by the higher costs of the stent and protection device equipment. Another problem with endovascular treatment is the greater potential for restenosis of the treated artery compared with surgery, although the clinical significance of this is not clear.

The carotid stenting versus carotid endarterectomy trials have consistently shown an excess rate of stroke after stenting for recently symptomatic stenosis compared with endarterectomy. In a pooled analysis of the European-based trials, the overall risk of stroke or death within 30 days of stenting was 7.7% compared with 4.4% after endarterectomy (risk ratio 1.74; 95% CI, 1.32–2.30).[39] However, there is a small excess of myocardial infarction after endarterectomy (risk <1%) and cranial nerve injury.

However, in symptomatic patients, the risks of stroke or death associated with the procedure were identical after stenting and endarterectomy in patients younger than 70 years, while all the excess risk of stroke appeared to be associated with older age. A more recent North American trial, CREST, showed very similar results. Hence stenting may be an option for younger patients. However, although the long-term effectiveness of stenting at preventing stroke recurrence appears similar to that of endarterectomy, there is an increased risk of restenosis after stenting and more long-term data are required to determine how often this leads to symptoms. Trials are examining the role of stenting for asymptomatic carotid stenosis. Stenting is also an option for treatment of symptomatic carotid stenosis in patients not suitable for endarterectomy, for example, stenosis secondary to radiotherapy, fibromuscular dysplasia, dissection and high cervical lesions not amenable to surgery.

Vertebral and intracranial arterial stenting

Surgical access to the vertebral artery origin is difficult and procedures carry high morbidity. Stenting therefore provides a preferable option for the treatment of symptomatic extracranial vertebral arterial stenosis, which most commonly occurs at the vertebral artery origin.[40] Stenting of intracranial arteries, for example basilar or middle cerebral artery, carries a risk of vessel dissection or rupture in addition to the risk of embolization of fragments of plaque. Stenting of these vessels is therefore usually reserved for patients with recurrent symptoms despite medical therapy. However, the benefits are uncertain and randomized trials are needed to establish the benefit of endovascular intervention for vertebral and intracranial stenosis.

Intracranial and subarachnoid haemorrhage

Spontaneous intracerebral haemorrhage

A typical history is given of sudden onset of severe headache, with the subsequent rapid development of focal neurological deficit. However, headache may be absent and in some cases the deficit progresses more slowly, sometimes over several days, especially when the haemorrhage is associated with anticoagulation or a coagulopathy. Intracerebral haemorrhage may also present as collapse. No one clinical feature reliably differentiates haemorrhage from infarction and imaging is essential to distinguish between the two.

Spontaneous intracerebral haemorrhage (ICH) may be divided into those occurring in the absence (primary) or presence (secondary) of an identified underlying structural abnormality. ICH is also associated with oral anticoagulant therapy. In this situation, tissue damage is limited by rapid identification of the condition and reversal of anticoagulation, although treatment dilemmas arise when the patient is anticoagulated for a high-risk condition such as acute pulmonary embolism or prosthetic heart valve. Consideration may have to be given to the eventual reintroduction of anticoagulation despite haemorrhagic risk or alternative strategies such as the placement of an inferior vena caval filter for DVT.

The initial management of cerebral haemorrhage is broadly similar to that of ischaemic stroke, apart from decisions regarding antiplatelet and anticoagulant therapy, which are clearly contraindicated. However, further investigation, including some form of angiography, should be undertaken in selected patients to exclude an underlying vascular abnormality which may require surgical or neuroradiological intervention to reduce the chances of a recurrent bleed. An intracranial aneurysm or arteriovenous malformation (AVM) should be particularly suspected in the younger patient with cerebral haemorrhage. Risk factors such as hypertension promote bleeding from aneurysms and AVMs and therefore should not necessarily influence the decisions about further investigation. The latter should be made after discussion with a neurovascular team at the local neuroscience centre.

Poor prognosis is conferred by a large volume of blood, intraventricular extension or reduced level of consciousness at the time of presentation. However, patients are often referred to neurosurgical colleagues for consideration of intervention and evidence has been sought in randomized controlled trials for this aggressive approach. The STICH trial recruited 1033 patients from neurosurgical centres with supratentorial intracerebral haematoma over 2 cm in diameter, occurring within the previous 72 h and randomized to early surgery or initial conservative (medical) management.[41] The results showed that 26% of the surgical group had a favourable outcome (good recovery or moderate disability on the Glasgow Outcomes Scale) compared with 24% of the conservative treatment group. This small difference between the groups did not reach statistical significance. However, there was a suggestion that patients with haematomas 1 cm or less from the cortical surface were likely to have a favourable outcome and these patients are being included in the second STICH trial.[41]

Cerebellar haemorrhage may present with occipital headache, truncal ataxia and conjugate gaze palsy, followed after an interval by impairment of consciousness and subsequent neurological deterioration as an expanding haematoma compromises the ventricular system, causing hydrocephalus and brain herniation. Surgical evacuation of a cerebellar haematoma is a life-saving measure.

Subarachnoid haemorrhage

The incidence of subarachnoid haemorrhage (SAH) is ~ 6 per 100 000 per year.[42] Bleeding into the subarachnoid space is often the result of rupture of an intracranial aneurysm. There may be a familial component to aneurysm development, but hypertension and smoking are the predominant risk factors for aneurysmal rupture. As in intracerebral haemorrhage, presentation is typically with sudden onset of severe headache, which may be accompanied by nausea and vomiting, neck stiffness, visual disturbance, altered conscious level and collapse. Subarachnoid bleeding may also be the result of trauma, dural fistula, arteriovenous malformations (AVMs) or cerebral venous thrombosis, or no clear cause may be found.

SAH is frequently fatal, with mortality rates in many series around 35–65%.[42] A significant proportion of the survivors remain dependent and complications such as delayed cerebral ischaemia secondary to vasospasm, rebleeding of the affected vessel and the development

of hydrocephalus may lead to a poorer outcome. At the time of presentation, outcome appears to be predicted by Glasgow Coma Scale score, age and the volume of intracranial blood. However, non-aneurysmal perimesencephalic haemorrhage, in which the bleeding is confined to the basal cisterns around the midbrain and there is no extension of the haemorrhage to the lateral Sylvian fissures or to the anterior part of the interhemispheric fissure, is associated with a good outcome. The cause is uncertain.

CT of the head is the preferred initial investigation and the pattern of bleeding may suggest a site of origin. CT angiogram may be added to this to localize the site of bleeding and identify a target for acute intervention. In the well patient, if clinical suspicion for SAH remains despite the lack of evidence on brain imaging, then lumbar puncture should be undertaken to look for xanthochromia. Lysis of the red blood cells in the cerebrospinal fluid (CSF) produces oxyhaemoglobin and bilirubin, giving a yellow colour to the CSF after centrifugation between 12 h and 14 days after SAH. MRI imaging with gradient echo T2 sequences or the FLAIR technique can also demonstrate SAH accurately. MRI is most useful in the setting of delayed presentation, with negative CT but positive lumbar puncture where a site of bleeding is sought.[42]

Management of SAH should be discussed with the neurovascular team at the local neuroscience centre and consists of treatment to secure the aneurysm or other source of bleeding and the prevention of secondary cerebral damage. Neurosurgery may be considered for those patients with an intracerebral haematoma secondary to SAH or surgical ventricular drainage for those who develop hydrocephalus. Surgical solutions to prevent rebleeding include operative clipping of the aneurysm, but there is increasing use of endovascular exclusion of the aneurysm using platinum coils. The ISAT study demonstrated lower morbidity and mortality after endovascular coiling compared with neurosurgical clipping for aneurysms suitable for both treatments.[43] The only agent shown in a randomized trial to prevent cerebral ischaemia after SAH is nimodipine, a calcium channel antagonist, continued for 3 weeks.[44] The oral or nasosgastric enteral route is preferred over intravenous administration to avoid precipitating hypotension. Its effect in reducing cerebral vasospasm may be the mechanism for the reduction in risk of a poor outcome.

Discussion

Acute stroke can be a devastating disease and the safe and effective evidence-based management of this condition and its consequences is fundamental to the practice of the geriatrician. Stroke is a medical emergency and early presentation of symptoms with prompt recognition by healthcare providers will allow the patient to be considered for treatments that limit disability or improve outcome, such as intravenous thrombolysis. Subsequent multidisciplinary care in a stroke unit will allow access to the best medical management of risk factors, reducing the risk of recurrent stroke, allowing timely further investigation and permitting better access to rehabilitation therapies. Rare causes of stroke, such as cerebral venous thrombosis, should always be kept in mind because they may need different management.

If, during investigation, a tight carotid artery stenosis is discovered, there is good evidence to guide the patient's further management. Selected symptomatic patients benefit from carotid endarterectomy. Carotid artery stenting provides an alternative for patients considered at high peri-procedural risk of stroke from endarterectomy. All patients with TIA or stroke who might be suitable for surgical or endovascular treatment should therefore be investigated for carotid stenosis, initially with non-invasive methods.

Intracranial haemorrhage, including subarachnoid and cerebral haemorrhage, is likewise a threat to life. Those patients who survive an intracranial haemorrhage without major disability may need further investigation to determine the presence of a treatable aneurysm or AVM.

NICE stroke guidelines with key priorities for implementation are given in Table 57.10.

Table 57.10 NICE stroke guidelines – key priorities for implementation.[10]

- In people with sudden onset of neurological symptoms, a validated tool, such as FAST (Face, Arm, Speech Test), should be used outside hospital to screen for a diagnosis of stroke or TIA
- All people with suspected stroke should be admitted directly to a specialist acute stroke unit following initial assessment, either from the community or from the A&E department
- Brain imaging should be performed immediately for people with acute stroke if any of the following apply:
  - indications for thrombolysis or early anticoagulation treatment
  - on anticoagulant treatment
  - a known bleeding tendency
  - a depressed level of consciousness (Glasgow Coma Score <13)
  - unexplained progressive or fluctuating symptoms
  - papilloedema, neck stiffness or fever
  - severe headache at onset of stroke symptoms
- On admission, people with acute stroke should have their swallowing screened by an appropriately trained healthcare professional before being given any oral food, fluid or medication

Key points

- Acute stroke is a major cause of death and disability in the older population.

- Selected patients benefit from thrombolysis after early brain imaging to distinguish between infarct and haemorrhage.
- Multidisciplinary care in a stroke unit improves outcome.
- Early treatment of severe carotid artery stenosis may prevent recurrent stroke.
- Patients with stroke and TIA should be managed as emergencies by a specialized stroke service to prevent early brain damage and recurrent stroke.

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CHAPTER 58

Stroke and stroke rehabilitation

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Introduction

Stroke is the leading cause of severe disability in most of the developed world. The World Health Organization (WHO) estimated that in 2002, 15.3 million people had a stroke worldwide, with more than one-third, 5.5 million, resulting in death.[1] Population projections for Europe suggest that the proportion of the population aged 65 years and over will increase from 20% to 35% by 2050, and this demographic shift will increase the number of acute stroke episodes from 1.1 million to more than 1.5 million per year by 2025.[2] In addition to a high mortality, stroke is also associated with significant disability amongst survivors. Nearly 40% of stroke survivors had severe and 20% had moderate disability, which consumed nearly one-third of all healthcare resources in a large community study in patients over 80 years of age.[3] Stroke is also an expensive disease. The estimated average cost of a stroke varies between countries and the average ranged from US$468 to $146 149 in a review of 120 studies across the world.[4] The average cost of stroke varied between $2822 in Eastern Europe and $12 883 in Japan to $22 377 in the UK, $24 548 in Sweden and $28 253 in the USA.[5] These costs do not take informal costs of care into account; when such costs are included, the total cost of stroke nearly doubles.[6] An estimation of total costs of stroke using a long-running community-based South London Stroke Register estimated that stroke costs in the UK totalled £9 billion per year with productivity losses due to morbidity and mortality accounting for £1.3 billion.[7]

Recent years have seen several developments to improve the management of stroke patients and reduce mortality, disability and costs associated with this disease. These range from advances in imaging techniques which improve diagnostic capabilities[8] and acute interventions aimed at reducing the size of brain injury[9] to improved acute care[10] and organized rehabilitation aimed at reducing residual dependence.[11] Despite the proven efficacy of thrombolysis and optimism about physiological manipulations in the acute phase of stroke, these interventions will have only a modest impact on eventual outcome in most stroke patients because of the limitations on their use.[12] On the other hand, over 300 randomized controlled trials provide a sound foundation for evidence-based practice in stroke rehabilitation, supplementing and often confirming decades of clinical experience.[13] Hence early and planned multidisciplinary rehabilitation remains the cornerstone of stroke management in the foreseeable future because it is applicable to most stroke survivors and has a strong evidence base for effectiveness in all patients, regardless of stroke severity.

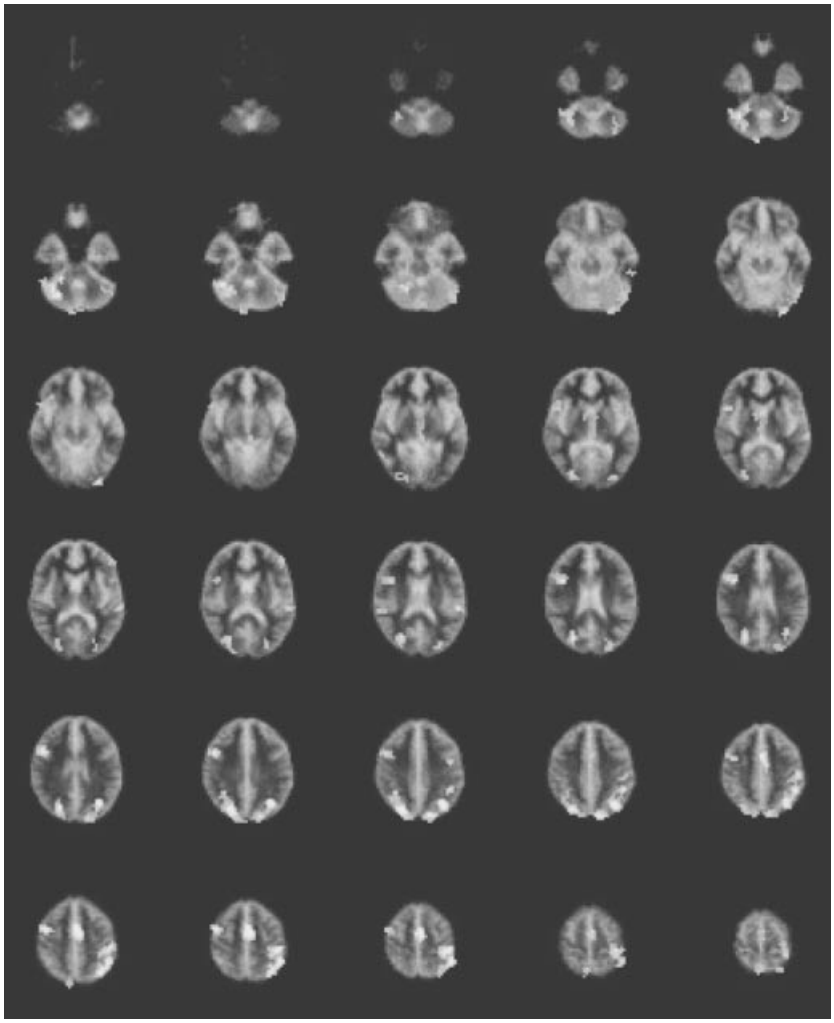
The neurological basis of recovery

The principle that underlies all rehabilitation is that the brain has an inherent capacity to recover lost function after stroke.[14] This is based on observations that most survivors regain some or many of the functions initially lost as a result of the stroke. Recovery is of two types: intrinsic, which involves neuronal regeneration and setting up of new axonal connections, and adaptive, in which alternative strategies, usually behavioural changes, are used to overcome disability.[15] The majority of patients show both intrinsic and adaptive recovery, the proportion of each being dependent upon factors such as age, severity of stroke, cognitive abilities and rehabilitation input after stroke. Intrinsic mechanisms consist of restitution, which includes repair of partially damaged pathways, and strengthening of existing pathways, mediated by local changes in blood flow, neurogenesis and cell migration, growth factor release, metabolism or neurotransmitter concentrations. Diaschisis or substitution is the development of new, but functionally related, pathways in the unaffected areas of the brain to take over the lost function. Studies in experimental models have shown a number of cellular and histological changes, such as axonal sprouting and formation of new dendritic connections, in the unaffected hemisphere of chronic stroke models, which probably are responsible for long-term recovery in these animals.[16] The

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

degree of recovery due to intrinsic mechanisms is variable and may be incomplete in a significant number of patients. In these circumstances, re-education in compensatory techniques, either by changed use of the affected side or retraining of the unaffected side, becomes an important behavioural adaptation to improve function and reduce the level of disability posed by the impairment.[17]

The development of advanced neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (MRI), has helped to demonstrate the processes of reorganization of neural activity after stroke in human subjects.[18] These studies have shown that unilateral motor tasks are associated with activation (increased metabolic activity) primarily in the contralateral sensorimotor cortex and the ipsilateral cerebellum in healthy subjects (Figure 58.1). The contralateral premotor cortex, ipsilateral somatosensory cortex and bilateral supplementary motor areas also participate in hand and finger motor tasks, particularly when the task increases in complexity. In recovered stroke patients, activation on these tasks is seen in the peri-infarct cortex and supplementary areas of the affected side (Figure 58.2) and also in additional regions including the ipsilateral sensorimotor and premotor cortex (Figure 58.3). The cerebellum, thalamus and prefrontal areas play an important part in restoration of function. The process of reorganization is dynamic, there is an evolution of changes with time and several different patterns have been



Group brain activation map in 5 subjects showing activation of the cerebellum,superior temporal gyrus, prefrontal cortex, SMA, PMC, lateral premotor cortex and somatosensory cortex on performance of the CRT

Figure 58.1 Activation on functional MRI during a choice reaction task (CRT) in a normal subject.

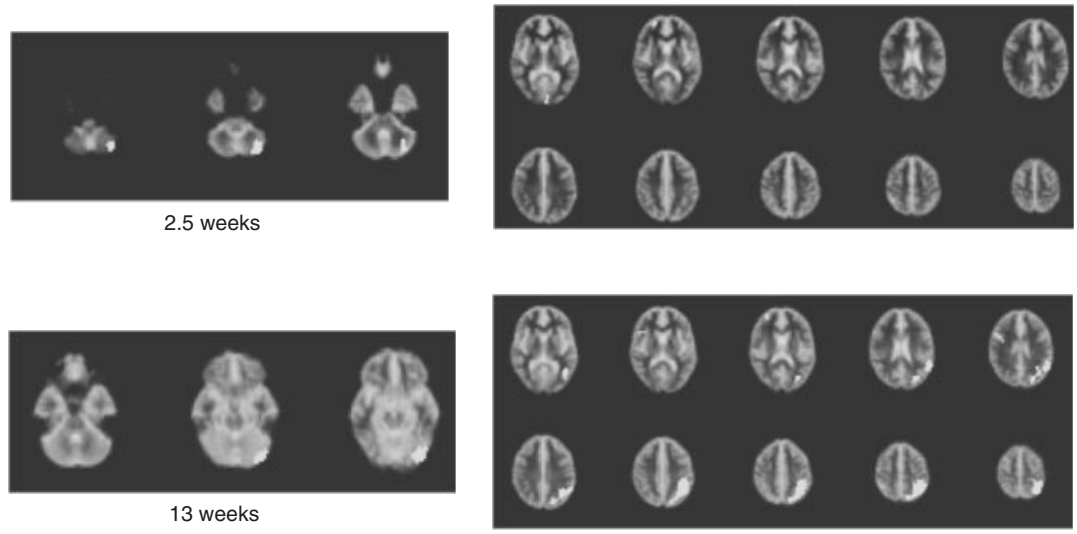


Figure 58.2 FMRI on CRT using affected hand in a patient with small lacunar infarct in the left internal capsule.

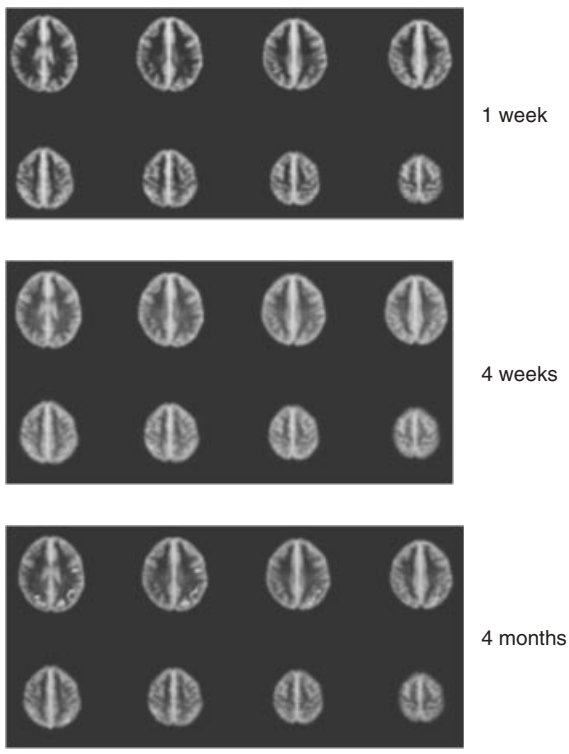


Figure 58.3 FMRI on CRT using affected hand in a patient with cortical infarct in the right hemisphere.

described. These include activation, and later extinction, of bilateral cerebellar and prefrontal areas, an initial increase followed by a decrease in activation of motor areas and progression from early contralesion activity to late ipsilateral activity.[19–22] All these changes appear to be associated with recovery, although their exact significance and relevance to recovery remain a subject of debate. It is now clear that there are multiple motor circuits in the brain which serve similar functions. Conventional pathways dominate in healthy subjects and inhibit the activity of alternative pathways in other areas of the brain. Disruption of traditional pathways in cerebral ischaemia reduces or eliminates the inhibition normally exerted by these pathways and allows activation of alternative pathways in the premotor areas of the affected side and primary motor areas on the unaffected side. Hence the paradigm for function has shifted from strict cerebral localization to that of interactive functioning of diverse cortical areas activated by the constantly changing balance of inhibitory and excitatory impulses.

New evidence suggests that neurogenesis represents a key factor in plasticity of the normal brain in response to environmental stimuli and that newly generated nerve cells form synaptic contacts which become fully integrated into existing neuronal circuitry.[15,23] Stroke-induced neurogenesis takes place in the subventricular zone and ischaemic boundary of adult human brains and has been demonstrated even in elderly patients up to 90 years of age.[24] Ischaemic injury to the brain sets up orchestrated waves of cellular and molecular events characterized by a

reduction in growth-inhibitory molecules and activation of growth-promoting genes by neurons. Angiogenesis appears to be the first step in regeneration, closely followed by the production and migration of neural progenitors.[25] Neural progenitors interact with other cells such as the astrocytes and oligodendrocytes and other growth factors, creating a microenvironment which promotes neurite outgrowth that repair damaged connections or establish new signalling pathways.[25]

An important concept in rehabilitation is that of 'brain plasticity', which implies that it is possible to modulate or facilitate reorganization of cerebral processes by external inputs.[23,26] This concept is supported by studies which show that activation can be facilitated by sensory stimulation, repetitive movement of the affected limbs or the use of drugs which modify neurotransmitter release.[27–29] Absence of adequate external inputs may have a negative effect – primate studies have shown that lack of afferent stimulation because of loss of voluntary activity impedes recovery in function after induced ischaemic injury to the brain.[30,31] The timing and intensity of intervention may also be important. Although some studies have suggested that very early attempts at intensive movement training in experimental models result in an increase in the size of the cortical lesion,[32] the bulk of evidence supports the benefits of early initiation of rehabilitation in animal models.[33] This emerging picture fits in well with theoretical concepts about motor learning, which emphasizes the importance of repetition, attention and goal-directed activity.

The observations made in animal experiments provide increasing support for some of the basic underpinnings of stroke rehabilitation, that is, that the earlier rehabilitation is started the better the recovery is, that greater intensity of treatment translates into greater recovery and that improvement can continue for some time after discharge from hospital or rehabilitation centre.[34] Feys *et al*., using a randomized controlled design, showed that adding an early, repetitive and targeted stimulation to the arm during the acute phase after a stroke resulted in a clinically meaningful and long-lasting effect on motor function in patients, even after 5 years of observation.[35] A meta-analysis of the effects of augmented exercise therapy after stroke has shown that such treatment has a small but favourable effect on activities of daily living (ADLs) within the first 6 months after stroke.[36] Intensive language training has been shown to improve language functioning significantly and this correlated with cortical perilesional reorganization or plasticity.[37] In an observational study, Bode *et al*.[38] investigated the importance of therapy content and intensity after controlling for stroke severity and found that content and amount of therapy are important predictors of greater than expected gains in self-care and cognition. A small functional MRI study demonstrated that drugs can modify reactivation and recovery; a single dose of fluoxetine resulted in significantly greater activation in the ipsilesional primary motor cortex and significantly improved motor skills on the affected side in patients with pure motor hemiparesis.[39]

To summarize, advances in basic sciences and clinical research are beginning to merge and show that the human brain is capable of significant recovery after stroke, provided that the appropriate treatments and stimuli are applied in adequate amounts and at the right time. There is also evidence to suggest that advances in pharmacotherapeutics and robotic assistive technology can further enhance and hasten the process of recovery, and will change the focus of rehabilitation from intuitive methods employed at present to new strategies firmly rooted in the neuroscience of recovery.

Patterns of recovery

Recovery is fastest in the first few weeks after stroke, with a further 5–10% occurring between 6 months and 1 year. About 30% of survivors are independent within 3 weeks and by 6 months this proportion rises to 50%.[40] Late neurophysiological recovery can continue for several years but is at a much slower rate and seldom results in dramatic changes in overall functional ability.[41] Completeness of recovery depends largely on the severity of the initial deficit. The more severe the initial deficit, the less likely is it that complete recovery will occur. The pattern of recovery is not uniform and shows considerable variation between individuals and also between different deficits in the same individual. There is currently no validated method for predicting the precise mode or degree of recovery for a given individual. In addition, there can be considerable variation in day-to-day progress of individual patients, which may mask overall recovery or at times give rise to false optimism. This problem can be overcome by monitoring patients over time, as overall trends are more important than 'one-off' assessments. Recovery may be affected adversely by the development of stroke-related complications. Comorbidity in elderly patients is another variable that affects overall recovery and rehabilitation.

The rate of recovery varies for different impairments and disabilities. Some problems, such as homonymous hemianopia, dysphagia and sitting balance, resolve very quickly in stroke survivors, whereas arm paralysis and language impairment recover more slowly and less completely. Perceptual problems may persist or take a very long time to recover. If all stroke survivors are considered, 62% are independent in self-care at 3 months and 66% at the end of 1 year, despite the persistence of neurological deficit in some patients.[42]

Objectives of rehabilitation

Rehabilitation in stroke is not simply a matter of being treated by a therapist or a group of therapists but involves a whole range of approaches to managing disability, provided by a coordinated multidisciplinary team and tailored to restore patients to their fullest possible physical, mental and social capability.[43] The goals of rehabilitation are to:

- maximize patients' role fulfillment and independence in their environment within the limitations imposed by underlying impairment and availability of resources;
- make the best possible physical, psychological and social adaptation to any difference between the roles desired and the roles achieved following stroke;
- ensure the long term wellbeing and quality of life of stroke survivors and their families by providing the necessary knowledge, skills and support using a range of health, social and voluntary services resources.

An important objective of the rehabilitation process is to monitor the relevance, quality and effectiveness of the services provided in order to ensure that they meet the expectations of patients and their families and obtain the best possible value for the money and effort being expended.

The revised WHO International Classification of Impairments, Disabilities and Handicaps (ICIDH) provides a conceptual model for stroke rehabilitation.[44] In this model, the terms disability and handicap have been replaced by limitations in activities and restriction in participation. The focus of attention shifts from pathology to handicap and from patient to environment during the course of rehabilitation.[45] The key areas that rehabilitation impacts upon are limitation of activity (disability) and restriction of participation (handicap). Disability is the lack of ability to perform an activity in the manner, or within the range, that the person was able to accomplish prior to the stroke and relates to function. In this context, the ability to undertake basic activities of self-care is fundamental to any physical rehabilitation programme. Handicap is the social consequence of disability and constitutes the limitations faced by stroke patients in fulfilling their normal role in society. It is not always possible to differentiate handicap from disability and most pragmatic approaches tend to combine these two dimensions, referring to them as social disability.

Rehabilitation in stroke is essentially a multidisciplinary activity, which has been described as a problem-solving educational process focusing on disability and intended to reduce handicap.[46] The basic principles that should be applied throughout rehabilitation of stroke patients are:

- documentation of impairments, disabilities and handicaps and, where possible, measuring them using simple, valid scales;
- maximization of independence and minimization of learned dependency;
- adopting a holistic approach to patients that takes into account their physical and psychosocial background, support mechanisms and environment;
- supporting caregivers and helping them to develop physical and psychological skills to provide long-term, sustainable support to stroke patients.

Process of rehabilitation

Rehabilitation has four important components: assessment, planning, intervention and evaluation.

Asessment

Assessment is fundamental to ascertain the precise nature and severity of deficits and define treatment goals prior to commencement of a rehabilitation programme because it provides a logical basis for treatment and management of stroke patients. The major reasons for undertaking assessments in stroke patients are to:

- define the type of patient, the extent of disability and the potential for recovery and/or responding to intervention (prognostication);
- identify main areas of difficulty and their underlying causes and also the expectations of the patient and the family;
- monitor the process of rehabilitation (evaluation) and assess the degree of recovery or residual disability at the end of the rehabilitation process (outcome).

A large number of neurological, physical and functional assessments are currently available and can be divided into global assessments (which determine the overall impact of stroke) and specific assessments (which deal with a single level or domain of impairment or disability). Composite scores for global disease severity are unreliable because of the dominance of speech and language function over other indexes and because, when very different disabilities are combined into one score, much specific information is lost.[47] Most scores also mix a variety of impairments and disabilities without considering their interactions.

The importance of knowing what information is wanted and why, that is, the purpose of a measure, is central to choosing any measure in rehabilitation. It is also important to decide on the least amount of information needed to achieve this purpose. The necessary characteristics of suitable measures are validity, reliability, sensitivity, simplicity and communicability. It is best to use existing measures wherever possible provided that they are valid for the purpose in mind, reliable in the circumstances proposed and relevant to the objectives of intervention. Moreover, the use of established measures makes communication and interpretation of data easier.

Predicting when a stroke patient has reached their full potential for recovery and may not benefit from further

therapy inputs is an imprecise science. Estimation of the functional capacity for recovery is particularly important for chronic stroke patients (more than 1 year after stroke), especially as these are the patients most likely to be denied further rehabilitation inputs. Unfortunately imaging and electrophysiological techniques to aid such predictions have generally proven to be expensive and unhelpful in clinical practice. However, it may be possible to combine these modalities to develop algorithms for patient selection for both research and clinical programmes. A recent example of this is the combined use of transcranial magnetic stimulation (TMS) and MRI to determine the integrity of corticospinal tracts and predict functional recovery potential.[48] The study showed that motor evoked potentials to TMS in the affected limb in the presence of little or no asymmetry in the fractional anisotropy map of the internal capsule on MRI (indicative of minimal long tract damage) was associated with a potential for improvement up to 3 years after stroke.

Planning

Planning is the process of goal setting based on identification of aims, objectives and targets.[49] Goals can be set at different levels; most patients will have immediate goals which relate to basic personal ADLs such as achievement of sitting balance, independent transfers and independence in toiletting activities. As patients continue to improve, goals need to be set for higher levels of function which incorporate not only independence in household activities but also the ability to undertake social, leisure and occupational pursuits. The ultimate goal of the rehabilitation programme is to improve overall wellbeing and participation, but many rehabilitation programmes often stop once patients have achieved independence in personal ADLs. It is important that planning takes into account not only the immediate needs of the patients but also their potential needs when they return to their own environment. This often involves adapting rehabilitation to the home setting and addressing the needs of caregivers, many of whom will play an important role in providing ongoing support and management of disability at home.[50] The areas of practical importance in goal setting are:

- *Accommodation*: Where will the patient live and what physical adaptations will be needed?
- *Personal support*: What is the level of support available for existing caregivers and what extra help will be essential for the patient?
- *Life satisfaction*: What roles will the patient be fulfilling within their social setting and how will they be occupying their time?

Many difficulties arise in stroke rehabilitation because the goals of intervention are not set in advance or because these goals have not been discussed and agreed on by all relevant parties. Goals of rehabilitation vary according to the expectations of those involved. The goal of hospitals may be to discharge patients as soon as possible, whereas the goal of patients may be to return to their previous functional status even if this is unattainable. The goal of caregivers may be to minimize the level of input that they need to provide even at the cost of institutionalization. Many of the difficulties ultimately faced in managing patients and in evaluating the effectiveness of interventions can be traced back to conflicts between the goals and objectives of different parties. An essential function of the whole rehabilitation team is to identify and modify unrealistically high (and sometimes unjustifiably low) expectations of patients and their families by making them more aware of the nature of residual deficit and expected prognosis as soon as these are reasonably clear. The two major problems that arise in goal setting include failure to use a common language in communication between various professionals or between professionals and patients and, second, failure to agree on a time frame within which the rehabilitation process must be accomplished.

Intervention

The minimum requirement of any stroke intervention is to provide care necessary to maintain the status quo and prevent deterioration of the patient's condition or functional ability due to poor management or complications. Further intervention should be aimed at facilitating recovery and improving outcome by minimizing disability and preventing handicap. Although large amounts of time and resources are devoted to various therapy interventions after stroke, evidence suggests that these resources are not used optimally in many settings and many of the potential gains of therapy input are not realized because of organization and systems limitations.[51,52] There is also limited evidence on individual interventions because despite the large number of studies available, most of them have small and heterogeneous samples, small amounts of formal therapy have been given in any trial and the interventions most often become a comparison between different intensities of treatment. In addition, there is considerable diversity of outcome measures used in these studies and limited comparability of study designs.[53]

At present, there are many rehabilitation techniques available, some with more robust evidence than others in trial conditions, but none that have been shown to be superior to any other in the major areas of physical therapy or in speech and language function in clinical practice. A summary list of current approaches is given in Table 58.1 and some of the more commonly used approaches are summarized.

Table 58.1 A summary of rehabilitation techniques in stroke.[54]

- **Early mobilization**
  - Key strategy associated with good functional outcomes
  - Meta-analyses over 55 years: no positive independent benefit
  - Not harmful for most stroke patients
- **Restoration of motor function**
  - Balance and motor therapy ± sensory feedback effective for function and mobility
  - CIMT clinically relevant improvements in arm motor function
  - Robotic devices
- **Neuromuscular stimulation**
  - rTMS associated with function recover in motor deficit, visuospatial neglect or aphasia
- **Motor imagery**
  - Positive effect arm function, promise for leg function
  - Virtual environments and tasks
  - Effects greater when combined with conventional therapy
- **Spatial Neglect**
  - Spatial techniques have limited success (prism adaptation)
  - Generalized attention enhancing techniques may be better

Early mobilization

Early mobilization is a key rehabilitation strategy associated with good functional outcomes in several observational and controlled studies.[55] Despite this, mobilization protocols remain poorly defined and vary across units and across patients. A review which combined data from observational studies and meta-analyses was not able to find any positive, unequivocal benefit associated with early mobilization, independent of other aspects of stroke care,[56] but concluded that early mobilization after stroke was not harmful for most stroke patients and may contribute as part of the routine stroke unit in achieving good long-term outcome in stroke patients.

Restoration of motor function

Restoration of motor function is a primary objective of stroke rehabilitation and there are several pooled data analyses of studies on various strategies for improving motor performance in stroke patients.[57] A prospective meta-analysis of the effectiveness of bilateral movement training in post-stroke motor rehabilitation showed that bilateral movements alone or in combination with auxiliary sensory feedback were effective in improving functional and mobility outcomes in stroke patients.[58]

Treadmill training has been shown to improve gait and walking speeds significantly in hemiparetic patients when used as an adjunct to conventional treatment. There are many approaches to gait training, but the most effective combination of training parameters, such as amount and timing of body support during the gait cycle, belt speed and acceleration, remains unknown.[59] The applicability of treadmill training in clinical practice is limited by the availability of specialist equipment and the technique may be suitable for only a small proportion of young stroke patients with relatively modest impairments.

Constraint-induced movement therapy (CIMT) has been one of the most important and well researched therapeutic approaches to restoring motor function. CIMT is based on the assumption that immobilization of the unaffected side to prevent learned 'non-use' and promote use of the affected limb results in faster (and more complete) recovery. The most convincing evidence for CIMT comes from the Extremity Constraint-Induced Therapy Evaluation (EXCITE) Trial.[60] The study showed that CIMT intervention in stroke patients was associated with statistically significant and clinically relevant improvements in arm motor function that persisted for at least 1 year. Despite this successful demonstration in a clinical trial, there continue to be doubts on the extent to which individualized CIMT is practical or cost-effective.[61] A meta-analysis has also suggested that recovery with CIMT is proportional to the amount of exercise given to the affected limb and it may be possible to achieve comparable benefits by less hazardous and less frustrating conventional therapy methods.[62]

Neuromuscular stimulation

Peripheral neuromuscular electrostimulation techniques appear to improve aspects of functional motor ability, motor impairment and normality of movement in recovering stroke patients.[63] A review of the use of repetitive transcranial magnetic stimulation (rTMS) in patients with post-stroke motor deficit, visuospatial neglect or aphasia showed that low-frequency rTMS to restore inhibition applied over the unaffected hemisphere or high-frequency rTMS to reactivate hypoactive regions applied over the affected hemisphere were associated with functional recovery.[64] There was great variation regarding the number of rTMS sessions required for a sustained effect and the timing of rTMS application after stroke.

Motor imagery

In recent years there have been several small clinical studies exploring the concept of motor imagery in stroke rehabilitation.[65] Most tasks involved mentally rehearsing movements of the arm and intervention periods varied from 2 to 6 weeks. The meta-analysis of these studies shows that mental practice has a positive effect on recovery of arm function and may have promise for improving leg function after stroke. The effects of motor imagery training appear even greater when combined with a conventional stroke rehabilitation programme in subacute stroke patients.[66]

Spatial neglect

A major advance in neglect rehabilitation is the shift of the conceptual paradigm from a spatial lack of awareness to a more generalized reduction in attentional abilities.[67] Non-spatial attention training has been shown to be associated with improvements in neglect, underpinned by changes in cortical activation pattern areas known to be associated with attention.[68] The clinical implications are that it may be possible to overcome spatial neglect in stroke patients by interventions that improve generalized or sustained attention. The expectation is that these techniques may prove to be more effective and have a more sustained effect compared with conventional spatially oriented methods which did not result in sustained improvements in neglect that could be transferred to functional tasks.

Organized (stroke unit) care

Evidence suggests that organized care, such as that provided in stroke units, both facilitates neurological recovery and expedites discharges.[69] The conceptual rationale for organized stroke care is the awareness that stroke affects several domains of human performance and results in multiple impairments, many of which have significant interactions in determining the level of disability.[46] It is also clear that no single discipline has all the skills, resources and expertise required to manage all aspects of recovery from stroke. Facilitation of recovery is further compounded by the different speeds at which impairments recover, as discussed previously, demanding a staged approach to interventions and therapy inputs. Rehabilitation goals are also shaped by personal needs of stroke patients, the environment they will return to and the personal support available after discharge. Hence the complex interdisciplinary process of stroke rehabilitation requires a multidisciplinary approach and collaborative policy of coordinated delivery of treatments based on comprehensive assessments and delivered by staff trained in stroke management in consultation with patients and their caregivers. This level of coordination of care is another argument to support the development of organized stroke services.[70]

The last two decades have seen a number of randomized controlled trials that suggested that organized care offered advantages to patients with stroke. However, many of these studies were too small to demonstrate a robust statistical benefit. Hence the Stroke Unit Trialists' Collaboration (SUTC) was set up to pool data from these and other ongoing studies from Australia, North America and Europe.[71] Despite the variations methods of organized care and patient selection criteria, the meta-analysis of pooled data from 29 trials which include 6536 patients shows odds reductions in mortality of 0.86 (95% CI, 0.71–0.94), death or dependence of 0.78 (95% CI, 0.68–0.89) and death or institution of 0.80 (95% CI, 0.71–0.90) at 1 year associated with organized care, which are independent of age and gender.[72] More importantly, and in contrast with thrombolysis for acute stroke, these benefits are seen for all stroke patients regardless of stroke aetiology or the duration between stroke onset and intervention. This expectation of the translation of trial efficacy into clinical effectiveness in mainstream practice has been further demonstrated in longitudinal studies.[73,74]

One of the difficulties faced in the interpretation of the evidence is that organized stroke care, especially stroke units, may mean different things to different people.[71] Definitions vary from 'a team of specialists who are knowledgeable about the care of stroke patients and who consult throughout a hospital or the community wherever a patient may be' to 'a geographic location within the hospital designated for stroke and stroke-like patients who are in need of medical and rehabilitation services and the skilled professional care that such an unit can provide'. There is also considerable controversy about the number and diversity of disciplines that need to be involved in stroke care and differences in staff composition between different settings have limited the generalization of findings in individual settings.

There are also difficulties in assessing the independent benefits of different types of organization of stroke care, mainly because the comparators for organized care in different studies range from general medical wards to different types of organized care. This heterogeneity of comparisons makes it difficult to determine if one type of stroke care organization is superior to other methods of organizing stroke care, as there is no common yardstick against which the benefits of different strategies of stroke care can be measured. Langhorne has shown that there is a definite benefit associated with comprehensive and rehabilitation stroke units and mixed rehabilitation units, all of which show an odds ratio (OR) of 0.85–0.89 in favour of organized care.[75] There may also be a possible benefit with acute (semi-intensive) units, although this just failed to achieve statistical significance (OR 0.88; 95% CI, 0.76–1.01). Mobile stroke teams were associated with no benefit in this analysis (OR 0.98; 95% CI, 0.95–1.05). There are no trials of acute intensive care, so this strategy of organizing stroke care remains untested. However, a review of the data suggests that emphasis on acute intensive care alone may not be adequate to change overall outcomes and that continuity of care is needed to realise the full potential of organized stroke unit care.

The amount of formal therapy received by stroke patients is small even in specialist stroke units. An important paper reported that patients spend more than 50% of their time in bed, 28% sitting out of bed and 13% in therapeutic activities and are alone for 60% of the time during the therapeutic day, even in a stroke unit.[76] The impact of a rehabilitation culture

on therapy input was elegantly illustrated in the CERISE study, a comparison of stroke rehabilitation units across four settings in Europe.[77,78] The study showed that motor recovery outcomes after stroke varied significantly across Europe and were not proportional to the therapy resources allocated to stroke but determined by the actual amount of treatment provided to stroke patients. For example, although the greatest amount of therapy resources being committed to stroke rehabilitation in the UK compared with other centres (70 h per week), stroke patients received the least amount of therapy input (1 h per day) compared with others. Stroke patients in the UK spent nearly 65% of the therapeutic day sitting, lying or sleeping and had greater contact with visitors compared with therapists. In contrast, therapy input in Germany was structured and strictly timed, resulting in significantly more time being spent with patients and with the best outcomes in Europe.

To summarize, there is consensus that well-organized and well-planned rehabilitation guided by well-defined goals based on adequate assessment and sensitive negotiation with patients and caregivers and provided on a specialist unit reduces disability and long-term institutionalization. There is, however, little evidence supporting any specific treatment technique for stroke patients. A pragmatic functional approach individualized for each patient's needs is recommended and strict adherence to theories with little scientific basis or clinical evidence of effectiveness should be discouraged. There is evidence suggesting that early, intensive intervention by therapists may speed recovery and hasten discharge from the hospital without increasing the total amount of therapeutic input. However, observational studies suggest that therapy time may not always be optimally deployed and rehabilitation can be made more effective and efficient by addressing issues around the process of rehabilitation.

Evaluation

Evaluation is the process of monitoring a patient's progress (or lack of it) and assessing the effectiveness of the rehabilitation process itself. Objective assessment of effectiveness of stroke rehabilitation has proven difficult for several reasons. These include the confounding effect of spontaneous recovery from stroke and difficulty in defining the extent of need and perceptions of good outcome, which may vary with the perspective of different observers. The wide variety of impairments and disabilities associated with stroke, and alsos the large number of instruments available to measure each impairment and disability, have also contributed significantly to the lack of a common assessment for outcome in stroke rehabilitation. A sensible approach is to use simple assessments more frequently during the rehabilitation process to monitor and adjust the treatment programme. A review of studies on stroke rehabilitation has shown the predominance of (ADL scales in monitoring rehabilitation.[79] This may be because the level of independence in ADL is not only the basis for more complete recovery but is also important in determining the care needs of, and resource use by, patients who continue to be dependent. Widespread use of ADL scales is further supported by the general agreement on the core ADL components (bladder and bowel function, feeding, cleanliness, dressing and mobility), high inter-rater reliability in clinical settings which is not influenced by the method of data collection and communicability within multidisciplinary teams. On the other hand, ADL scales blur the distinction between impairment and disability, have a low ceiling effect and cannot identify the reasons why patients fail to achieve goals.

There is little consensus on the most relevant outcome, the method of measurement or the most appropriate timing of such assessment in stroke patients.[45] The perception of a favourable outcome may vary depending upon professional, patient or carer perspectives and how long after stroke it is assessed. Although it has been recommended that outcomes should be measured at different levels within the ICIDH framework, patients will value their ability to undertake desired activities or to participate in social roles more than improvements in specific areas of performance. Even within the ICIDH framework, the rate and extent of change may vary between the different levels and continue over months. Consequently, it is important to consider the timing of any assessments and the influence of factors known to affect the chosen outcome measures. Measures at the level of activities (disability) are widely used for outcome and have the advantage of objectivity, reliability and sensitivity besides being simple and relevant to the patient. Measurement of participation and quality of life, however, may be more relevant and appropriate over the longer term. Appropriate timing of assessments is important and the natural history of recovery from stroke must be considered when selecting the time of assessment. Spontaneous recovery, especially in patients with greater severity of stroke, may not plateau until 6 months after the event. Most experts agree that 6 months is the most appropriate time point at which to measure neurological and functional outcome. Wider interactions with environment and society become important after this stage and measurement of participation, life satisfaction and emotionality should preferably take place at a time when the patient's social condition has stabilized.

Common problems in stroke rehabilitation

Stroke-related disorders that are important during rehabilitation include visual problems (hemianopia or inattention), dysphagia with the risk of aspiration and infection,

communication problems, venous thrombotic disease, urinary and bowel problems, spasticity and contractures, pressure sores, shoulder pain, associated reactions, cold hemiplegic arm and oedema of the limbs. The main neurological complications include depression, seizures, behavioural changes and central pain. Stroke patients are also at a higher risk of falls, which, in association with osteoporotic bone changes in the hemiplegic limb, often result in fractures on the stroke side. Various studies have shown that complications occur in about 60% of stroke patients undergoing rehabilitation and are more frequent in patients with severe disability.[80]

Dysphagia

Dysphagia is a common complication of stroke; recent reviews show that its incidence ranges from 21 to 55% based on clinical tests and from 44 to 78% based on videofluoroscopy.[81] Although aspiration and dysphagia are not synonymous, many of the problems associated with dysphagia in stroke patients are because of aspiration and their close relationship means that there is considerable overlap between the assessment and management of these two conditions. In addition, a substantial number of patients have silent aspiration (aspiration without cough or any outward sign of difficulty) and are at an increased risk of developing complications because clinical swallowing assessments underdiagnose the problem and appropriate preventive strategies are not applied.[82] Dysphagia is associated with significantly higher mortality and morbidity in stroke patients, longer hospital stays, increased demands on feeding resources and higher admissions to nursing homes.[83] Evidence indicates that detection of aspiration and institution of appropriate management strategies reduce pneumonia, mortality, length of hospital stay and overall healthcare expenditure.[81] Dysphagia is also associated with malnutrition, poor participation in rehabilitation and worse functional outcome in survivors.[84,85] Although acute dysphagia improves in 80% of survivors, data from a 5 year follow-up of 1288 stroke patients in the South London Stroke Register showed that dysphagia at stroke onset was associated with a 3–5-fold increase in institutionalization at 5 years.[86] The prolonged duration of hospital stay, higher institutionalization and increased need for statutory support after discharge associated with dysphagia are estimated to cost the NHS £200 million per year.[87]

Videofluoroscopy is the gold standard for assessment of dysphagia[88] but is not a feasible screening option in clinical settings.[82] The water swallowing test is routinely used in clinical practice but its diagnostic accuracy has been questioned.[82] However, it is likely to remain the mainstay of bedside screening because it is safe, relatively straightforward and easily repeated.[89] Decreases in blood oxygenation during swallowing and reduced ability to clear airways of aspirate have been observed in dysphagic patients, suggesting that oximetry may help in the diagnosis of aspiration.[90] Direct flexible endoscopy of the vocal cords and aspiration is another technique available to clinicians but requires expertise and validation in larger clinical studies.[91]

Current management options for dysphagia are limited.[2,14] Compensatory techniques and dietary modifications under the supervision of speech and language therapists and dieticians remain the mainstay of treatment of dysphagia in stroke patients. Patients with persistent dysphagia require alternative means of nutrition [e.g. nasogastric tubes, percutaneous endoscopic gastrostomy (PEG)]. Other measures to alleviate swallowing problems include stimulation of the pharynx by mechanical or thermal means, cortical stimulation with magnetic fields to stimulate the swallowing reflex and insertion of artificial electrical pacemakers to trigger laryngeal elevation.

Dysphasia

Dysphasia is a defect in language function manifesting as impairment in speech production, comprehension, reading or writing in the absence of motor disturbances of voice production or writing, visual or auditory deficits and intellectual or cognitive impairment. Impaired ability to understand speech is common in dysphasic patients. The difficulty in comprehension increases with increasing linguistic complexity of the speech presented and length of sentences used. The extent to which a dysphasic patient can understand what is being said is frequently overestimated, which can result in misunderstandings between patients and their families or professionals involved in patient care. It is important that communication problems are identified early in stroke patients because many therapy interventions are dependent on this function.

The more severe forms of dysphasia are often easy to diagnose on clinical examination in most stroke patients. The diagnosis of mild dysphasia may be more difficult, especially if the patient has a high-level language deficit. It is also important to differentiate dysphasia from confusion secondary to cognitive impairment. Enquiries about the patient's language background (native language, profession, social and educational status), previous speech problems and hand dominance should be part of the examination. Problems in comprehension are particularly difficult to assess. A bedside measure can be obtained by assessing the patient's ability to respond to commands of increasing complexity, either in content or in linguistic structure. It should be remembered that in some patients errors may occur because of dyspraxia or memory problems. All patients suspected of having dysphasia should be assessed by speech and language therapists regardless of the severity of the impairment. Appropriate treatment

of dysphasic patients consists of individualized therapy programmes supervised by speech and language therapists, development of simple communication strategies to allow multidisciplinary rehabilitation and educating caregivers in communication techniques appropriate to the patient's level of impairment.

Perception

Perception is an important but neglected aspect of stroke management. The outcome of rehabilitation frequently depends on effective management of perceptual problems rather than on motor recovery alone. Despite this, perceptual problems are poorly understood and difficult to assess objectively because of the paucity of valid assessment instruments. Their management is equally difficult and a subject of great controversy. Perceptual problems after stroke can be divided into (i) neglect, which is the disregard ofm and failure to attend to, one half of external space; (ii) agnosias, which comprise problems with interpreting sensory data from the environment or the body (visual, tactile, autotopagnosia); and (iii) apraxias, the collection of problems involving formulating, initiating or sequencing motor activity. Visuospatial dysfunction can be particularly disabling in stroke patients, as it affects their ability to judge distances and relationships between objects or between self and objects in a three-dimensional setting, causing severe restrictions in daily living activities. Patients with anosognosia are also difficult to rehabilitate because of the lack of awareness of any problems.

It is not known whether these deficits respond to general stimulation or to specific remedial measures. Recent research suggests that neglect may be amenable to therapeutic interventions such as prism correction, electrical stimulation and increasing attentional activities, but further studies are required to confirm these findings. Although visuospatial problems delay or compromise functional recovery in most patients, some individuals eventually make a full functional recovery despite residual impairments. There is no effective treatment for apraxia. Management currently focuses on increasing the patient's awareness of the condition and its effects. This requires early recognition of the problem and teaching of adaptive skills and coping strategies to patients and their relatives.

Tone and spasticity

The management of muscle tone is an integral part of therapy input in stroke patients. Muscle tone as a dynamic, complex process that is part of an overall pattern of posture and movement which plays a vital role in recovery from stroke. Appropriate management of tone is one of the fundamental principles of the Bobath method of facilitative physiotherapy, which gives priority to normalization of tone and improving symmetry even at the cost of postponing standing or walking. However, this preoccupation with normalization of tone is not supported by evidence and there are several other approaches which combine early mobilization with active muscle tone management during rehabilitation.[92]

The management of abnormal tone and spasticity is difficult, as it depends on achieving the right balance between hypo- and hypertonia between different muscle groups. The problem is compounded by the fact that spasticity varies between different groups of muscles, times of day, emotional state of the patient, activity being undertaken and posture of the limb. Inappropriate exercise can result in inappropriate tone patterns to the ultimate detriment of the patient. If not managed correctly, spasticity leads to bad gait patterns, contractures and loss of function. Management of spasticity should be undertaken jointly by doctors and physiotherapists. Spasticity should be considered in relation to other impairments and in the context of therapy goals because interventions directed solely at reduction of spasticity are unlikely to result in significant functional gains.

Treatment of abnormal tone is initiated by physiotherapists, who can offer a range of interventions, including physical therapy, attention to posture and seating and conventional orthoses. Drug therapy can be used in conjunction with physical manoeuvres and adjusted to achieve optimum effects. Its main drawback is its lack of selectivity; since all muscle groups are affected equally, there may be undesirable hypotonia in some muscle groups (e.g. drugs for reducing spasticity in arm muscles may affect walking). In general, improvements in localized treatment of spasticity which can be administered selectively to specific muscle groups without major adverse effects have resulted in options such as baclofen and dantrolene being replaced by botulinum therapy.[93]

The focal injection of botulinum toxin inhibits the release of acetylcholine into the synaptic cleft, resulting in a reversible paresis of the muscles relevant for the spastic deformity. It has proven effective and well tolerated in several placebo-controlled trials for the treatment of focal upper and lower limb spasticity, although it has not been shown to improve motor function.[93] In a systematic review of 11 double-blind randomized placebo-controlled trials that included 782 patients, botulinum toxin reduced upper limb spasticity in patients post-stroke, but the improvement in functional ability was not established.[94] There were insufficient data to establish botulinum efficacy on lower limb spasticity.

Electrical stimulation techniques are a useful adjunct to other treatments, particularly for treating spastic equinus deformities. In some cases, phenol nerve blocks can produce good results, especially when standard treatments fail or botulinum toxin produces beneficial short-term

effects. In patients refractory to medical treatments, surgical interventions such as abalation of peripheral nerves, tenotomies or reconstruction of tendons and joints may be required.

The hemiplegic shoulder

Shoulder pain, restriction of movement and subluxation of the shoulder joint are common problems in stroke patients. In hypotonic patients, the loss of muscle strength around the shoulder joint and the weight of the paralyzed arm may result in malalignment of the humeral head in the shallow glenoid cavity, predisposing to inferior subluxation of the shoulder. There is considerable variation in the reported incidence of subluxation in stroke patients, but it is estimated that one in every five patients is affected. Shoulder pain is more common and inconsistently related to subluxation. It is encountered in rehabilitation settings with disconcerting frequency and may be a result of spasticity in the shoulder muscles, glenohumeral subluxation, reflex sympathetic dystrophy (the shoulder–hand syndrome) or orthopaedic causes such as rotator cuff injury, arthritis or adhesive capsulitis made worse by immobility. Contributory factors include careless handling of patients and incorrect position of the hemiplegic arm. Management should be undertaken in collaboration with physiotherapists and includes measures such as proper positioning of the arm during periods of inactivity, avoidance of abnormal arm movements which cause excessive strain on the shoulder joint or inappropriate pulling of the hemiplegic arm during transfers and early passive exercise to prevent joint stiffness and contractures. Treatment with analgesics, strapping, non-steroidal anti-infammatory drugs and steroid injections may help in some patients.

Depression

Estimates of depression in stroke vary widely and it is estimated that between 30 and 60% of stroke patients have clinically significant depression, the highest prevalence and severity occurring in the first 2 years after stroke.[95] Diagnosis of mood disorders in patients with acute stroke is difficult because changes in appetite, sleep or interest (all indicative of depression) may be a normal adjustment response to physical disability and changed roles. The diagnosis of depression in stroke is further hampered by the presence of dysphasia and impairments in attention or concentration which make assessment difficult. A pooled estimate from population-based studies of individuals who have had a stroke indicated a prevalence of depression of about 33% at any time during follow-up.[96] There are no precise estimates on severity of depression after stroke, although most patients seem to have minor symptoms of depression. Women, younger patients and those with greater disabilities are at a higher risk of developing post-stroke depression.[97] Post-stroke depression also appears to be more common in patients with a family or personal premorbid history of depression.

Post-stroke depression may last for 7–8 months or more without treatment and is highly correlated with failure to resume premorbid social and physical activities. Depression also has a negative effect on functional and cognitive recovery, integration into the family environment and caregiver stress in stroke patients.[98] There is growing evidence suggesting that early recognition of depression in stroke and early treatment with appropriate antidepressants can facilitate recovery.[99] Specific treatment strategies, including counselling, cognitive behavioural therapy and treatment with antidepressants, have been used for treating post-stroke depression with variable results. A systematic analysis involving 1655 patients with stroke who underwent treatment for depression after stroke showed some effect of pharmacotherapy (i.e. tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and others such as flupentixol/melitracen, reboxetine and trazodone) in improving mood but no effect on cognitive functions, ADLs or reducing disability.[100] Psychotherapy was ineffective in improving mood or overall functioning in patients with stroke and depression and had no effect on ADLs or social functioning.

Pain

Pain assessment in stroke patients can be difficult, but a population-based study has shown that nearly one-third of stroke patients have moderate to severe pain in the first few months after stroke.[101] Although pain improves spontaneously in most cases, it can interfere with physical therapy, interrupt sleep and contribute to depression. Post-stroke pain can be caused by pre-existing arthritis, decreased mobility, changes in gait and abnormal body posture. Patients with spino-thalamic involvement may develop a central post-stroke pain syndrome, which is often associated with sensory loss.[102] Central post-stroke pain syndrome can be difficult to treat but may respond to amitriptyline or gabapentin.

Fatigue

Many patients suffer from fatigue after a stroke, which can be long lasting and cause functional limitations. Although post-stroke fatigue has been attributed to depression, physical deconditioning, associated medical ailments and effects of medications are likely to be contributory factors.[103] Treatment of post-stroke fatigue involves treatment of underlying causes; no specific treatment has been shown to have any benefit.[104]

Psychosocial aspects

Stroke is a major life event which presents major difficulties for patients, their partners and their families. It not only may result in physical dependence but also requires a wide range of emotional and social adjustments within families, often leading to role reversals and establishment of new hierarchies.[105] The post-stroke phase is a period of considerable turmoil during which patients and their families need to be supported in order to achieve good outcomes. The reaction to stroke is akin to breavement; a phase of shock and despondency is followed by a period of positive thinking and optimism as patients focus on the activities of the rehabilitation team. Many patients and caregivers harbour unrealistic hopes of recovery and it becomes important for the clinician to prevent unrealistic expectations and pave the way to more successful adaptation to the reality of residual disability. People who were very active and independent prior to stroke feel distressed when they need to rely on others for even the most basic personal tasks. This loss of esteem may lead to apathy and even depression and is more likely to happen in the paternalistic environment of hospitals. The attitude and approach of the medical team are crucial in enabling the patient to maintain dignity. Esteem plummets when patients are not given much attention on hospital rounds or are depersonalized by staff who refer to them as 'CVAs' or 'hemis' rather than considering them to be unique individuals. Stroke patients may need counselling in addition to practical support to cope with the fears of disfigurement, loss of physical function, falls, poverty and an uncertain future after returning home. Alterations in personality may occur after stroke and are a source of great distress to partners and caregivers of stroke patients.

Conclusion

Stroke is a devastating illness and causes long-term disability which dramatically and irreversibly changes the lives of patients and their families. Although there is great optimism that improvements in preventive care and acute interventions will reduce the burden of stroke, their potential remains to be realized. Meanwhile, organized coordinated rehabilitation provided by specialists and in partnership with patients and their caregivers offers the only realistic hope of reducing disability and handicap after stroke. Despite its proven effectiveness, specialist stroke rehabilitation is not available to the majority of stroke patients who stand to gain from this input. Part of the problem is the lack of infrastucture, resources, staff and training to provide specialist care. This is compounded by the lack of awareness of the special needs of stroke patients and the benefits of dedicated rehabilitation among some professionals. Increased resources may be difficult to achieve in the short term, but improving the level of awareness amongst health professionals may prove a quicker, simpler and effective way of improving stroke outcome.

Key points

- Stroke is the leading cause of severe physical disability in adults.
- The brain is capable of significant recovery after stroke, provided that appropriate treatments are applied in adequate amounts and at the right time.
- Early and planned multidisciplinary rehabilitation remains the cornerstone of stroke management.
- Rehabilitation is a multidisciplinary problem-solving, educational process focusing on disability and intended to reduce handicap.
- Objectives of rehabilitation should include supporting and training caregivers in disability management.

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CHAPTER 59

Communication disorders and dysphagia

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Communication

Effective communication allows an individual to convey successfully a message or meaning to another person and for that meaning to be correctly interpreted. Communication is one of the most fundamental characteristics of higher cognitive functioning and is dependent upon symbolic encoding, either in sounds, script or gesture. These complex acts are supported by virtually every aspect of brain function, with the afferent sensory stimuli being processed through associated regions, being integrated with stored memories and emotions along with immediate factors relating to attention, arousal and motivation which can stimulate a verbal or gestural response governed by different environmental and behavioural conditioning.

In its simplest form, communication requires one individual to be able to receive a message from another, either auditorily or visually, to interpret this message and to generate an appropriate response which is encoded into sounds, gestures or written letters in order to respond. Thus, the term 'language' refers to a code used to represent and communicate ideas and feelings. Language may be verbal or non-verbal, for example, written words, sign language, gestures. However, all modes are governed by rules shared within cultures. Speech is the verbal expression of language which comprises of the meaning (semantics) and sounds (phonology). Language can also be expressed through writing using symbols (as in letters) or agreed body movements for signs (e.g. sign language or gestures).

Ageing and communication

There is evidence that language is an inherent capacity and that the neural basis for language is not only a dynamic process but prewired biologically.[1] Researchers have investigated the capacity for language in different animal species and although some animals, particularly apes, can be taught to use symbols, humans appear to be specifically, physically and neurologically adapted for the integrated neurocognitive requirements for complex speech and language. Much work has been done on the development of language from birth during its rapid acquisition stage. Less work has been conducted examining the effects of ageing on communication processes later in life.[2] However, it is clear that changes in vision and hearing, laryngeal function and cognitive function impact upon the effectiveness of communication. For example, less cognitive agility may reduce the facility to make inferences when complex language structures are used; the use of stereotypical phrases to fill in language when original vocabulary is less easily accessed and a slight deepening and huskiness in the voice may all be associated with normal communication changes associated with age. Many of these will be subtle and will not be evident in casual conversation.[3]

The impact of age-associated changes on the sensory systems is likely to have a profound effect on communication, but it is difficult to define exactly when the normal deterioration in hearing and eyesight becomes pathological and affects communication more extremely.[4]

Hearing

The prevalence of hearing impairment depends upon the criteria used to define it. However, many studies have indicated that between 30 and 40% of older people (over the age of 70 years) have a hearing loss of 25 dB hearing level. This level would affect the ability to hear normal conversation. Although men are more likely to have more severe hearing level loss than women, increasing age is by far the major determinant in predicting who is likely to have a hearing difficulty. A decrease in overall hearing acuity is often accompanied by disproportionate difficulty in discriminating higher frequency sounds and a lowering of the threshold at which sounds cause discomfort. These age-related changes are called *presbycusis*. Distortions of the speech signal result in misinterpretation and misunderstanding, which have implications for easy and effective communication and also cognition and mood.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Hearing loss can be profoundly isolating and reduce enjoyment in many activities, and is frequently associated with depression.[5] For many elderly individuals, communication problems and related psychosocial difficulties resulting from hearing impairments could be reduced significantly by the use of hearing aids.[6] However, a high proportion of those provided with hearing aids do not use them. One study indicated that only 21% of hearing-impaired elderly individuals provided with a hearing aid used them. Improved usage is associated with an education programme accompanied by the provision of a hearing aid. This should include information on how physically to manipulate the aid itself in addition to giving encouragement to develop the necessary tolerance in order to become accustomed to the different auditory input provided through a hearing aid. Thus, provision of a hearing aid is not an end in itself and is unlikely to lead to successful improvement in communication.[7]

Vision

This chapter would be incomplete without mentioning the contribution of vision to communication but, as this is less central, only an outline is given. Visual changes occur with age and affect depth perception, colour sensitivity, the ability to focus and the ability to adapt to changes in lighting. In addition, a number of visual impairments, such as cataract, glaucoma and macular degeneration, are associated with increasing age. Vision obviously affects reading and writing, but reduced ability to see gestures and facial expressions or to recognize people can impair the communication process in a more subtle manner.[8] One of the concerns to speech and language therapists is that visual and hearing impairments can profoundly affect an individual's response to rehabilitation of acquired dysphasia or dysarthria. Detailed speech and language assessments usually require reasonable vision and hearing; hence patients with defects in these may be more difficult not only to treat but also to evaluate and diagnose.

Cognition

Age-related cognitive decline is examined in depth elsewhere in this book.

There is a close relationship between thought and language and it has been suggested that various types of cognitive decline, including specific dementia types, lead to fundamentally different communicative symptoms. However, with cognitive decline, pragmatic dysfunction leading to incompetence in communicative processes is more frequently evident than linguistic difficulty. Thus, a person may have appropriate language structure, but may use the language in a way that does not communicate effectively, either by ignoring the context, lacking coherence or showing difficulty in sticking to a topic.

Studies have indicated that certain cognitive abilities, such as accessing vocabulary, may be insensitive to age-related changes until the age of 75–85 years.[9] The main difficulty in normal ageing is associated with slowing of processing time and less resistance to distraction.[10] However the prevalence of dementia increases with age, rising from around 1% at age 65 years to 35% at 85 years. The rate of increase for both genders is marked throughout ageing.[11] It is estimated that 30% of those with dementia do not get a diagnosis, particularly in the young onset group (aged under 65 years) who are usually diagnosed late in the course of their dementia.[12]

Dementia can be seen as going through three stages, progressing from mild, through moderate to severe loss of function. Language can be affected at each stage, causing difficulties in understanding and expression and may, along with memory problems, be an early indicator of the condition. Individuals may demonstrate word-finding difficulties, particularly for objects and people's names, and use empty phrases (i.e. without meaning). Additionally, the individual has difficulty in focusing on a topic of conversation and may start in the middle of a topic, with no reference to the listener's knowledge or understanding of the subject. This difficulty in providing relevant information for the listener causes communication to break down and is frequently misunderstood by the communication partner.[13,14]

Persons with age-related cognitive disorders affecting communication can be assisted by speech and language therapists. The therapist will undertake a differential communication assessment and advise the patient and carers on strategies to improve effectiveness of interaction. These strategies include reducing the use of pronouns such as 'he' or 'she' and referring to people or things by name; avoiding open-ended questions, for example, giving definite options; encouraging gesture and using communication prompts such as pictures and charts.[15]

A review of recent research indicates that multi-modality intervention that included physical exercise, volunteer work and exercises to help memory and language can have beneficial effects provided that participants are physically able to complete the intervention. The training of caregivers of patients with Alzheimer's disease about the disease, communication strategies and the use of memory books and wallets can help to improve their communication interactions with patients with Alzheimer's disease.

Motor speech

The power and range of movement may be affected by age; this can subtly change respiration, phonation and articulation, allowing the listener frequently to identify a

speaker that they cannot see as being older or younger. The voice becomes less robust with the onset of tremulous, frail or a thinned quality. It is possible that these changes are associated with some adaptation of the laryngeal cartilages, thickening of the vocal folds and reduction in respiratory support.

Depression

There is a high prevalence of depression in older people and this has been found to be higher than that of dementia.[16] It has an impact on communication, leading to reduced communication, less interest in the communication of others and a general withdrawal from social groups. Depression has been associated with grieving over loss of functions (such as hearing and physical dependence), loss of autonomy and control over life, loneliness and anxiety about the future. Depression can be so profound that it can mimic a cognitive dysfunction or aphasia and in all cases will mean that rehabilitation of another specific communication disorder will be rendered more difficult. Identifying whether depression is a component of the communicative disorder is essential as its treatment can assist with general management of other physical deficits.

Diagnosis and assessment of communication disorders

The specific communication disorders associated with age-related pathologies, such as stroke, progressive neurological disease or dementia, are dysphasia, dysarthria and dyspraxia. Dysphasia is commonly a consequence of left-hemisphere stroke which can also give rise to dyspraxia. Dysarthria is more commonly a symptom with bilateral hemisphere damage or damage to the cerebellum or extrapyramidal system as a consequence of head injury, brain tumour or progressive neurological diseases such as Parkinson's disease.

Dysphasia

Dysphasia is a disorder of language which affects the ability to understand or to express oneself in speech or writing. While the term 'aphasia' denotes a greater severity, the terms are now frequently used interchangeably. Dysphasia is usually of sudden onset and results from focal brain damage. One-third of stroke survivors are affected by aphasia and between 30 and 43% of those affected will remain severely affected in the long term.[17]

Traditionally, aphasia has been classified according to localization theory. Wernicke aphasia is correlated with damage to the left posterior region of the perisylvan cortex or primary language area. A lesion in this area frequently produces disturbances of auditory comprehension, inability to repeat and name objects, but with the preservation of verbal fluency. Paraphasic errors and indefinite pronouns pervade expressive language of Wernicke aphasic patients, who often retain inappropriate, but rich, intonation. In contrast, Broca aphasia is classically associated with lesions localized to the left anterior region of the perisylvan cortex. Broca aphasia is associated with less disordered comprehension, severe word-finding problems and marked impairment of fluency. Thus, the patient will give the appearance of struggling for speech. Studies have indicated that the more profound, debilitating aphasia (Wernicke) is associated with increasing age. Thus, a high proportion of stroke patients over the age of 80 years will have Wernicke aphasia profoundly affecting their comprehension ability. One of the hypotheses for this age-related shift in aphasia type is that cerebral damage has a more posterior focus with advancing age, which could be associated with aetiological changes.

More recently, speech and language therapists have adopted a cognitive neuropsychological model for diagnosing and managing dysphasia as this approach is of more direct assistance in planning and targeting therapeutic intervention. This model is based on the assumption that the language system is organized in an integrated and modular manner and that this can be selectively impaired by brain damage. Thus, once the particular modules have been identified by assessment, then treatment can either stimulate the use of this linguistic deficit or teach strategies to overcome or bypass that aspect of the system. Much research, most of which is based on single case studies, has identified particular patterns of language associated with disruptions to the neurolinguistic structure and has reported varying degrees of success in focusing therapeutic intervention.[18–20]

There is no universally accepted treatment which can be applied to every aphasic person.[21] This is due to the great variation of persons with aphasia, in terms of symptoms and their severity, and in individual differences in lifestyle needs and preferences. A Cochrane review by Greener *et al*.[22] emphasized the importance of functional approaches to therapy, stating that 'The aim of rehabilitation in aphasia is primarily to maximise successful communication in day-to-day interactions' (p. 35).

In general, aphasia therapy strives to improve an individual's ability to communicate through multiple strategies by aiming to

- help the person to use remaining abilities;
- restore language abilities as much as possible by developing strategies;
- compensate for language problems;
- learn other methods of communicating;
- coach others (family, health and social care staff) to learn effective communication skills to maximize the aphasic patient's competence.

About half of recovery from stroke occurs within the first month, but it can continue up to 6 months post-stroke (according to Wade, 1997, cited by Greener *et al*.[22]) and beyond. Single and group case studies have demonstrated improvements in language recovery after many years post-stroke.[18,23,24] There is evidence for the potential of neuroplasticity in the brain, that is, the ability of the brain to use other regions for functions where the original region has been damaged and that early, intense treatment can enhance this.[17]

It is important for all healthcare professionals to be able to have a good understanding of the communicative ability of a patient with aphasia – particularly confidence in the level of comprehension, in order that the patient is engaged in decisions and engaged in giving informed consent appropriately. There are several bedside screening tests which can assist with identifying the level and nature of dysphasia, for example, the Frenchay Aphasia Screening Test.[25] The more formal speech and language therapy assessments provide a detailed description of the neurolinguistic and functional aspects of the aphasia which would inform speech therapy intervention, for example, the Comprehensive Aphasia Test.[26]

A review of recent research indicates that when all other factors (e.g. health, education and social status) are held constant, chronological age alone is not a good predictor of either severity or prognosis in aphasia, with some very elderly patients improving and recovering remarkably well. However, the risk of concomitant problems is greater with increasing age and these may well contribute to a less good outcome. For example, patients who have aphasia alongside age-related memory problems or hearing loss provide more challenges to rehabilitation.

A recent Cochrane review of the impact of speech and language therapy for persons with dysphasia[27] along with two meta-analyses[28,29] indicate that speech language therapy is effective for people with aphasia. There are features of therapy that may make treatment more successful, for example, timing, intensity and involvement of family and friends. More intense therapy of longer duration results in greater gains for aphasic individuals. There seems to be little difference between different types of aphasia therapy. Family and volunteer involvement is successful and results in better outcomes for individuals with aphasia. Laypersons can be effectively trained to deliver some aphasia therapies. Novel computer-based therapies can reduce therapist time, are acceptable to patients and effective. Augmentative and alternative communication (AAC) devices can be successfully used with aphasic individuals, some of whom may be more suited to the use of such devices. It is important to remember that the effectiveness of therapy relies strongly on patient participation and motivation.

The use of computers to deliver therapy to people with aphasia is growing in popularity. Many studies indicate that language treatment can be made accessible for frequent practice and can be adapted to address different deficits and language styles and can implement structured approaches to neurolinguistic learning. Single case and group studies using both qualitative and quantitative methodologies indicate encouraging progress with computer-delivered treatment.[30] Additionally, there is growing recognition relating to the social consequences of aphasia to the patient and the family and increasing evidence that a holistic life-long approach to support a person with aphasia improves the quality of life, preventing isolation, depression and withdrawal from society.[31]

Assessment of mental competence and comprehension is important in some cases where the need for informed consent, power of attorney or testamentary capacity is being considered. While observation and subjective opinion may lead to a particular conclusion, it is essential to support and/or test this with objective tests and consider other influences, for example, social pressures, perseveration, fatigue and poor attention span which may affect ability.[15]

Dyspraxia of speech

Dyspraxia of speech refers to the inability to carry out fine voluntary movements necessary for speech, while voluntary and automatic movements of the same muscles often remain intact. Thus, a patient may be unable to stick their tongue out on command but can lick their lips to remove a crumb (oral dyspraxia). Muscular weakness may be absent or insufficient to account for the speech difficulty and the patient may produce expletives or automatic speech (as in counting) clearly but is unable to imitate sounds and words (verbal dyspraxia). Speech is characterized by effortful groping and patients have difficulty in imitating and repeating sounds and words. Patients with dyspraxia frequently do not have difficulty with other oral motor tasks such as controlling saliva or swallowing, and this can help distinguish dyspraxia from dysarthria where those functions are frequently abnormal. Dyspraxia rarely exists without some degree of dysphasia and may lead to individuals being thought of as having more language impairment than is the case; it is primarily associated with cortical damage.

Dysarthria

Speech requires accurate motor programming, initiation and control of fine movements of the lips, tongue, palate and larynx, which act in harmony with timing of inspiration and expiration. This results in the precise articulation, pitch and tonal quality, resonance and phrasing which are associated with normal speech.[32] Impairment of the central peripheral nervous system can affect this choreography and produce a motor speech disorder termed *dysarthria*. Again,

Table 59.1 Speech symptoms associated with underlying pathology.

Type	Features
Spastic	Strained and hoarse voice, hypernasality and slow, imprecise articulation (Aronson, 1993, cited in Palmer *et al.*[33]). Often accompanied by swallowing and drooling difficulties[33]
Flaccid	Isolated areas of involvement depending on which motor neurone is affected (Enderby, 1983, cited in Palmer *et al.*[33])
Ataxic	Excess loudness, tremor and irregular articulatory breakdowns (Aronson, 1993, cited in Palmer *et al.*[33]). Intonation, pitch and volume can also be affected (Enderby, 1983, cited in Palmer *et al.*[33]), in addition to difficulty with alternate tongue movements
Hypokinetic	Breathy monotone voice with reduced loudness (Enderby, 1983, cited in Palmer *et al.*[33]) and articulation tends to be accelerated and imprecise (Yorkston *et al.*, 1999, cited in Palmer *et al.*[33])
Hyperkinetic	Features strained hoarseness and voice arrests
Mixed	Similar symptoms to spastic dysarthria and tends to be accompanied by a wet-sounding voice with rapid tremor, poor laryngeal and tongue movements and poor control of lips (Enderby, 1983, and Aronson, 1993, cited in Palmer *et al.*[33])

the term anarthria usually indicates a more severe form of the disorder.

The different types of abnormal speech can indicate the level of underlying neurobiological dysfunction (see Table 59.1).

Traditionally, speech and language therapists have managed dysarthria by assisting in differential diagnosis, treating the speech problem and preventing secondary complications by facilitating participation in normal activities (Yorkston, 1996, cited in Sellars *et al.*[34]). Evaluation of speech and language therapy of this kind of group has been deeply problematic given the heterogeneous nature of the underlying impairments, making single case studies the most usual method for evaluation. Frequently people with dysarthria benefit from augmentative or alternative communication methods.

Augmented and alternative communication

Augmentative and alternative communication (AAC) refers to any system of communication that is used to supplement or replace speech, to help people with oral communication impairments to communicate. For individuals with aphasia or dysarthria, this could range from 'low-tech' aids such as drawing and writing or communication books, to 'high-tech' aids such as computerized voice output communication aids.

The objectives of introducing AAC to a patient with an acquired communication problem is to maximize their communicative function in the areas of life that are seen as a priority by the patient and to continually review the changing needs of the patient. It is necessary to[35]

- identify participation and communication needs;
- assess capabilities in order to determine appropriate options;
- assess external constraints;
- find strategies for evaluating the success of interventions.

To ensure appropriate access to the range of resources available, individuals who may benefit from communication aids should have access to an AAC specialist or team, who are skilled in assessment, planning, intervention and continuing support in this area.

Swallowing

The normal swallow

Swallowing involves a process of transporting saliva, food and drink from the mouth to the stomach and it involves the protection of the respiratory system from being entered by anything other than air. Normal swallowing is easy, quick and unconsciously performed, but it is a highly complex process carried out more than 1000 times per day in normal adults just to clear saliva from the mouth to the oesophagus. In the one second that it takes to swallow to clear the mouth of saliva, over 40 paired muscles are used.[36] The mouth, nose and pharynx are passages for food and air in addition to being involved in speech. The mechanisms for using these pathways appropriately can be affected by central and peripheral neural or structural damage. Swallowing necessitates cessation of respiration with closure of the airway, while the pharynx is being used to transport saliva, liquids or foodstuff. Alterations in tone, pressure or timing can cause aspiration, that is, the leakage of food or fluid into the airway. This will commonly cause coughing or choking as the system acts in a coordinated fashion to expel the foreign material and return it to the pharynx. However, silent aspiration can occur where food or liquid does not stimulate coughing or choking and penetration of the material is unimpeded.

Oral phase

Swallowing is frequently described as having three phases, the oral phase, the pharyngeal phase and the oesophageal phase. In the oral phase, sometimes termed the preparatory phase, food is taken into the mouth, chewed and moved back to the opening of the pharynx. The lips seal the

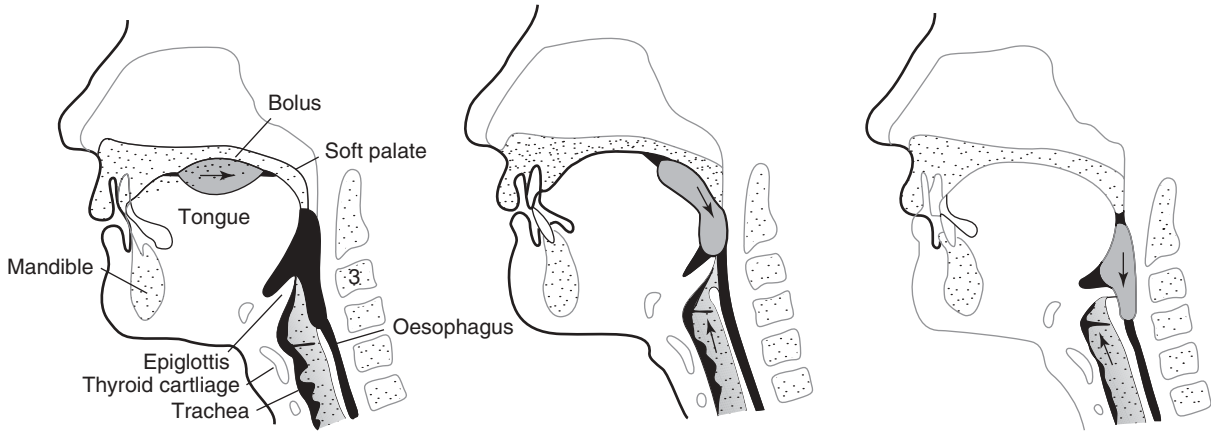

Figure 59.1 Normal swallowing process.

oral cavity and the hyoid rises. At the start of the oral propulsion phase, the soft palate will seal off the nose prior to the tongue propelling the bolus into the pharynx. The oral phase is mainly under voluntary control and can be disturbed if the lips are affected and unable to make a good seal – this delays the initiation of the swallow. Facial palsy can lead to some of the bolus being deposited within the buccal sulcus and poor tongue movements will result in poor bolus control (Figure 59.1).

Pharyngeal/oesophageal phases

The pharyngeal phase is considered to start when the bolus touches the posterior pharyngeal wall. The nasal pharynx is sealed more tightly through the raising of the soft palate and the laryngeal inlet is sealed through raising the larynx, closure of the vocal folds and tilting of the epiglottis. Descending movements of the pharyngeal constrictor muscles squeeze the bolus down. The oesophageal phase is seen as the last phase of swallowing; it is the involuntary transport of the bolus through the oesophagus to reach the stomach. Anatomically, the oesophagus starts at the upper oesophageal sphincter; this sphincter is frequently called the PE (pharyngoesophageal) segment or is otherwise known as the *cricopharyngeal sphincter*. This sphincter at rest is contracted and the bolus alone will not stimulate its release. It relaxes in concert with the pharyngeal bolus transport and opens in unison with the anterior movement of the larynx. This protects the pharynx from regurgitated food and prevents air from entering the oesophagus during breathing. The timing of the opening and closure of this sphincter can be problematic in many neurological diseases. If this sphincter is not released in a timely fashion, patients will complain that they have difficulty in pushing food down into their throat or they may have overspill aspiration with the bolus not clearing through the pharynx into the oesophagus before the airway becomes patent. The ageing process alone affects deglutition with an increase in chewing movements in order to form a bolus and to initiate swallowing, a slowed swallowing propulsion time and a reduction in pharyngeal and oesophageal peristalsis. There is evidence that, with increasing age, the normal elderly aspirate increasingly, but this may not give rise to any symptoms. The mechanisms for tolerating increasing aspiration are not fully understood. However, targeted assistance for those with dysphagia can reduce symptoms and improve weight gain and quality of life.[37]

Dysphagia

The broad term 'dysphagia' can encompass problems at the oral, pharyngeal or oesophageal stages of swallowing and should not be confused with difficulties with feeding or eating, which may be associated with anorexia, depression or other psychological problems or difficulties in transporting food from the plate to the mouth. Symptoms associated with dysphagia include choking during eating or drinking, difficulty in swallowing certain food types, an inability to swallow saliva, nasal regurgitation of food or drink and discomfort during swallowing. While dysphagia should not be defined by the presence or absence of aspiration, patients with feeding or swallowing problems need to be assessed in order to identify the risk of aspiration, as this is particularly associated with increased chest infections, pneumonia and mortality.

Persons with dysphagia are more at risk of malnutrition and dehydration along with aspiration that can lead to aspiration pneumonia. All of these complications can lead to poor outcome and can ultimately be the cause of death, but additionally there are profound social and psychological effects of swallowing disorders. Coughing and choking can be frightening for both the patient and carers. Dribbling/drooling can be socially offensive and embarrassing and have a severe effect on the quality of life of the patient.

Box 59.1 Bedside swallow assessment.

Risk indicators

- Weak, husky voice (dysphonia)
- Inability to cough voluntarily
- Weak cough – no effective expulsion
- Pooling of food or saliva in mouth/cheek
- Frequent coughing/choking even on saliva
- History of recent chest infection
- Complaints of difficulty with swallowing
- Reports having to gulp/or abnormal sensation
- Reports difficulty with some types of food

Observation

Try teaspoons of water, and if successful try teaspoons soft purée, and then if successful try foods with more substance

Observe:

- Patient reports negative sensation
- Poor lip closure/degree of leakage
- Untimely or absent elevation of larynx
- Residue in mouth following swallow
- Lack of clarity of voice, following swallow
- Choking/coughing before, during or after swallow

Clinically, dysphagia is common with 78% of people having had a stroke initially presenting with this symptom and a high percentage of those with dementia and progressive neurological disease also having dysphagia. It presents a 'major diagnostic and therapeutic challenge'.[38] Interdisciplinary management of dysphagia is advocated[39]; the aim of this management is to protect the patient from complications of dysphagia, maintain adequate nutrition and ensure that patients and carers are fully aware of the nature of deficit and methods of managing the problems.

Assessment will in the first instance be done at the bedside (see Box 59.1) and will take account of the oral and laryngeal structures and movements, dental state, cognition, posture and other issues which can contribute to the safety of the patient to progress with oral feeding. It is important to note that the absence of the gag reflex does not automatically indicate a major swallowing problem, just as the presence of the gag does not indicate safe swallowing. Other factors, such as the bolus control, clarity of the voice (is it wet and gurgly after a test swallow?) and the effectiveness of the cough (is the cough firm and effective?) are all important. A therapist will frequently give different trial swallows of food substances (semisolid, firm, etc.) and liquid. Certain food substances may be more easily and safely transported and, therefore, there could be recommendations on the consistency of oral intake. If it is clear from the bedside assessment that there is a danger of aspiration, it may be necessary to request further assessment in a videofluoroscopy clinic which can determine more objectively the type and nature of the aspiration and whether positioning the patient or changing the consistency of the bolus can moderate such risk. However, there are certain guidelines that can assist with the management of any person with dysphagia. It is important to remember that it is very difficult to swallow safely if one is not fully conscious and aware. Furthermore, if a patient is unable to sit upright or cough purposefully, the likelihood of aspiration is increased. Any of above would indicate a necessity for more in-depth dysphagia assessment.

Videofluoroscopy to assess swallowing is not infallible. The procedure can produce both false positives and false negatives. For example, the trial swallows may not produce, at the time of recording, evidence of dysphagia which in some patients occurs only with fatigue after several mouthfuls – a false negative. However, on other occasions, aspiration may be observed, which is asymptomatic or induced by the tension of the situation or unpleasantness of the radiopaque material – a false positive. The indications from videofluoroscopy must be placed in the context of the history of the patient.

Some patients are able to eat certain food textures more efficiently and safely. For example, persons with either reduced oral sensation, buccal control or inadequate laryngeal lift may aspirate more on fluids rather than on semisolids. Fluids do not stimulate the swallow reflex so rapidly, cannot be formed into a bolus, overflow into the pharynx and larynx without needing propulsion and leak into larynx more readily. Therefore, some patients may be advised to avoid liquids, but may manage a soft puréed diet. Other patients may have difficulty in manoeuvring or forming a bolus due primarily to the involvement of tongue, lips and jaw and these patients may need to avoid foods that require chewing.

Problems with communication and/or swallowing are profoundly disabling to the patient and cause great anxiety to relatives. While some of these components may not resolve spontaneously or with treatment, they all deserve appropriate assessment and intervention aimed at improving the management of the symptoms, improving the quality of life by maximizing function and reducing secondary sequelae.

Key points

- Communication and swallowing impairments are profoundly disabling and impact upon the quality of life.
- Discriminating between dysphasia, dysarthria and dyspraxia is important for neurological diagnosis and therapeutic intervention.

- Patients need their level of comprehension to be assessed objectively by the speech and language therapist as it is frequently not what it seems.
- There is evidence that some patients continue to improve communication skills and swallowing function with therapy beyond the period of spontaneous recovery.
- Appropriate identification and management of dysphagia reduces mortality and morbidity.

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CHAPTER 60

Acute and chronic subdural haematoma

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Introduction

When Virchow first described '*pachymeningitis haemorrhagica interna*', subdural haematoma (SDH) was considered as a fatal disorder. Over the past 150 years, a dramatic improvement has been achieved due to better understanding of its pathophysiology, new imaging methods and refinement of operating techniques. However, the morbidity and mortality are still relatively high, especially in the elderly population.

The subdural space lies between the inside of the skull with the periosteal/meningeal dura and the arachnoid layer. That layer contains the cerebrospinal fluid (CSF) and the bridging veins, and surrounds the pia of the brain. This potential subdural space becomes a real subdural space when the dural border cell layer cleaves away from the inner meningeal layer.[1] Subsequently a subdural, or more precisely intradural, haematoma may evolve in that space. As the brain atrophies and pulls away from the skull, the strain placed on the meninges is relieved by a splitting open of the weak layer at the dura–arachnoid junction. Figure 60.1 is a magnified schematic representation of a subdural haematoma. The creation of such meningeal spaces in elderly individuals explains, in part, what sometimes appear to be spontaneous haematomas in this area of the meninges in this patient population.

Haematoma in that space can be either acute or chronic. To fill this potential space and cause pressure on the brain, a mass requires that the pressure applied is greater than the intracranial pressure (ICP), that is, >17 mmHg. Acute SDHs are mainly post-traumatic and of arterial or arteriolar origin. There are two common causes of acute SDH: parenchymal laceration and bridging vessel rupture. Parenchymal laceration represents a severe primary injury and the acute SDH worsens the clinical condition. Surface or bridging vessels might be ruptured during cerebral acceleration–deceleration due to violent head motion. Once the initial bleed has been initiated, the acute SDH becomes subacute and then can turn into chronic SDH. The difference between acute and chronic SDH was defined by McKissock *et al*. in 1960.[2] He denoted 'acute' those cases presenting urgent symptoms within 3 days of trauma, 'subacute' those presenting within 4–20 days and 'chronic' those presenting after 20 days.

In the elderly population, acute SDH has a high morbidity and mortality rate. However, although chronic SDH is common and treacherous, it is potentially treatable. Indeed, the drainage of a chronic SDH is one of the most rewarding and least demanding neurosurgical procedures.

Acute subdural haematoma

Acute SDH is a serious, life-threatening condition and its management is complex, especially in the elderly. Acute SDHs are mainly post-traumatic, but can also be spontaneous in the context of coagulopathy. According to McKissock *et al*.,[2] an acute SDH is diagnosed within 1–3 days after trauma. In severe acute SDH, neurological deficit occurs immediately. The mechanism of injury and also the outcome differ between age groups. In younger patients, most acute SDHs are caused by motor vehicle accidents and in older patients by falls.[3] It has also been shown that older patients have a higher mortality rate and that it is likely that age causes an alteration in the pathophysiological response of the central nervous system to severe trauma.[4] Because of the frequent association of acute SDH with parenchymal injury, surgical management decisions should take into consideration the recommendations for both lesion types. Spontaneous or non-traumatic acute SDHs in the elderly represent a specific clinical entity related mainly to coagulopathy, anticoagulants or antiplatelet therapy. This coagulopathy-associated acute SDH is prevalent in a particular group of patients in which the risk is associated with coagulopathy of one sort or of another.

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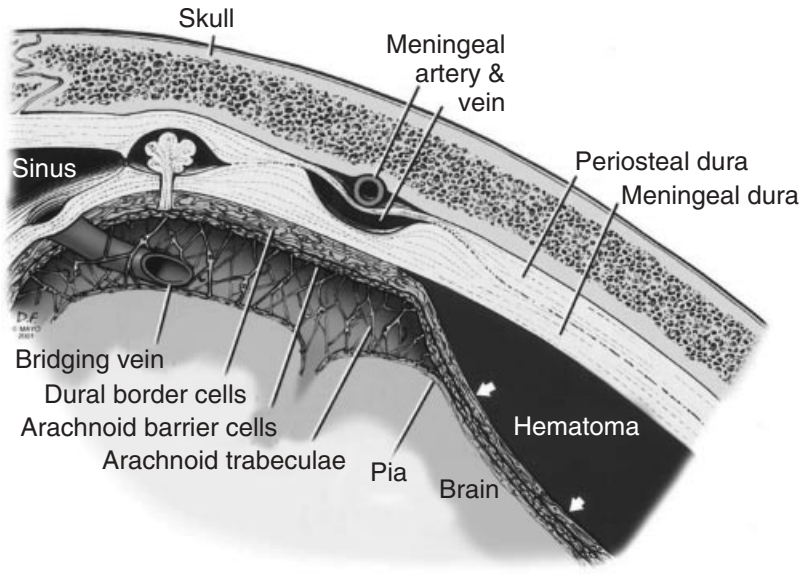

Figure 60.1 Schematic and magnified representation of a subdural haematoma. The dura has two layers: the periosteal dura located on the inner side of the skull and the meningeal dura towards the meninges. Underneath, the arachnoid layer with its trabeculae contains the CSF and the bridging veins. Between the arachnoid and the meningeal dura there is a dural border cell layer. The potential subdural space becomes a real subdural space when the dural border cell layer cleaves away from the inner meningeal layer. Subsequently, a subdural or more precisely intradural haematoma may evolve in that space. (Reproduced from Atkinson *et al. Journal of Magnetic Resonance Imaging* 2003;**17**:484–6, with permission from Wiley-Blackwell.)

Pathophysiology

There are various abnormalities predisposing a cortical artery to rupture: avulsion of an arterial twig branching at a right-angle from the parent artery, rupture of a small artery traversing the subdural space and connecting a cortical artery to the dura mater, termed 'bridging artery', or adhesions between a cortical artery and the dura mater or arachnoid.[5] An acute SDH is related to an arterial bleed in the subdural space. It has been shown that global cerebral blood flow is reduced after acute SDH, leading to a critical ionic imbalance with oedema and widespread cell death. Local pressure causes focal ischaemia, which leads to increased energy metabolism and reduced tissue oxygenation, which can cause infarction a few hours after acute SDH. Even after rapid decompression and haematoma evacuation (<4 h), many patients die. The majority of patients with chronic SDH must, at some time, have had an acute spontaneous SDH. Therefore, probably, many of the so-called spontaneous cases may have been the result of a brisk head movement not severe enough to be considered trauma or of an unrecognized or forgotten trauma. The recognition of spontaneous acute SDH as a clinical entity is important, since many of these patients may subsequently go on to develop chronic SDH.

Epidemiology

Studies conducted after the introduction of computed tomographic (CT) scanning have reported an incidence of acute SDH between 10 and 30% in patients admitted with severe traumatic brain injury. When including mild, moderate and severe head injuries, 11% present with acute SDH.[3] More than one-third of cases of acute SDH are in patients over 60 years old. Similarly, about one-third of cases of admitted head injuries in the elderly population will have an acute SDH.[6] Only 30–40% of acute SDHs requiring surgery are isolated lesions. In the majority of cases, an acute SDH is associated with other intracranial and extracranial injuries. Associated intra- and extracranial lesions have been reported in larger series to occur in 50% of patients presenting with head trauma and in 70% of patients with Glasgow coma scale (GCS) <10.[3]

Clinical presentation

Patients with acute SDH are most of the time comatose: 40–80% of patients had a GCS score of 8 or less.[3] A lucid interval has been described in 10–40% of patients before admission but there is no conclusive evidence that this correlates with outcome. Pupillary abnormalities are observed in 30–50% of patients on admission or before surgery. Acute subdural haematoma may be located along the falx, between the two cerebral hemispheres with the 'falx syndrome': paresis or focal seizures contralateral to the haematoma.

Investigation

CT scanning is the method of choice. On a CT scan, acute blood collection with a haematocrit >23% has a higher density than the brain parenchyma, that is, >80 Hounsfield units. Acute SDHs are classically hyperdense and crescent-shaped, with a concave surface away from the skull. However, they can have a convex appearance, especially in the early stage of bleeding. Subdural blood can also be seen as a layering density along the tentorium cerebelli and the falx. It is also important to identify the

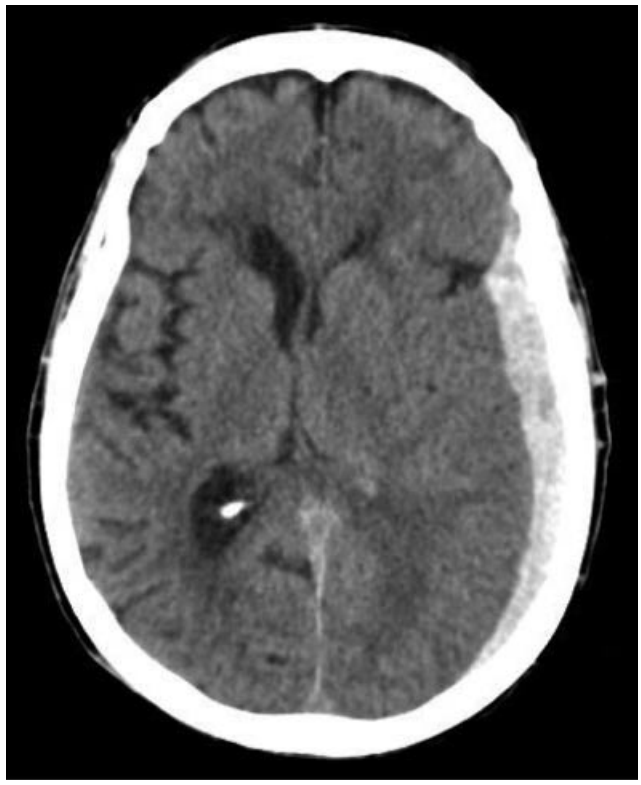

Figure 60.2 CT scan of a left acute subdural haematoma in an elderly patient. The hyperdensity is crescent-shaped with a concave surface away from the skull. Midline shift is inferior to the thickness of the haematoma.

brain parenchyma lesion such as intracerebral haematoma and contusion, subarachnoid haemorrhage, midline shift, brain swelling and skull fractures. An example of a left acute SDH is displayed Figure 60.2.

Management

Observation for a small acute SDH is usual. Surgery should be considered for progressive neurological deterioration. The main difficulty in the elderly population with acute SDH is to decide whether or not an old patient in a coma with an acute SDH should be operated on or not, as the morbidity and the mortality are known to be very high.

Small SDHs often do not require evacuation, as surgery may increase the brain injury if there is a hemispheric swelling with herniation risk through the craniotomy. Patients in a coma, that is, with a GCS score of 3–8, on initial presentation were found to be significantly associated with increased mortality and a poor outcome. Initial pupillary reaction was also shown to be a very important prognostic factor for outcome. For elderly patients with both pupils dilated and non-reactive to light an unfavourable outcome was predicted (death rate almost 100%).[3,7,8] Concomitant parenchymal brain lesions and traumatic subarachnoid haemorrhage were also predictive of a worse outcome, due to an increased intracranial pressure.[9] Studies also showed an increase in mortality with large haematoma; the survival rate dropped below 50% when the acute SDH thickness exceeded 18 mm. A midline shift of more than 10 mm was found also to be correlated with a high mortality. However, it is possible that patients older than 65 years tolerate a greater midline shift because of brain atrophy. The difference between the subdural haematoma thickness and the midline shift seems to be a very strong prognostic factor. In fact, a striking decline in the survival rate was found when the midline shift was greater than the haematoma thickness. When the midline shift was greater than the thickness of the SDH, that is, more brain swelling than SDH, the survival rate was less than 25%.[4] It has been suggested that all patients with acute SDH in a coma (GCS score <9) should undergo intracranial pressure (ICP) monitoring. Surgery is indicated only when ICP values are <40 mmHg owing to the poor outcome of elderly patients with high ICP monitoring.[3] In patients with acute SDH and indications for surgery, surgical evacuation should be performed as soon as possible,[3] but recent studies failed to show any significant difference in outcomes between patients undergoing early (<4 h) or delayed (>4 h) surgery.[4] The haematoma is usually evacuated with a craniotomy and subdural drainage or by decompressive craniectomy. A large craniotomy flap is often required to evacuate the thick coagulum and to gain access to possible bleeding sites. The actual bleeding site is often not identified at the time of surgery. Nevertheless, there is no statistically significant difference in the number of re-operations, irrespective of the chosen operative method (large versus simple craniectomy).

A management algorithm was developed based on clinical and CT parameters to predict the outcome of older patients with acute SDH and to indicate whether surgical haematoma evacuation should be performed.[4] This algorithm is represented schematically in Figure 60.3.

Trauma and emergency department clinicians encounter an increasing number of older patients with head injuries on premorbid antithrombotic therapies. These patients are at increased risk of acute brain lesions. In the setting of minor head injury, patients may not exhibit signs of overt bleed. Therefore, clinicians must weigh the risks and benefits of completing a head CT to rule out a subclinical haemorrhage. Currently, no studies have addressed the efficacy or utility of reversing anti platelet therapy in traumatic head injury with exogenous platelet administration. However, in warfarin-treated patients presenting with traumatic head injuries, clinicians should have a low threshold for obtaining a head CT to rule out acute intracerebral bleeding. Rapid reversal of anticoagulation to a near-normal profile may be warranted in CT-documented acute haematoma.[10] In these patients, the mortality is closely

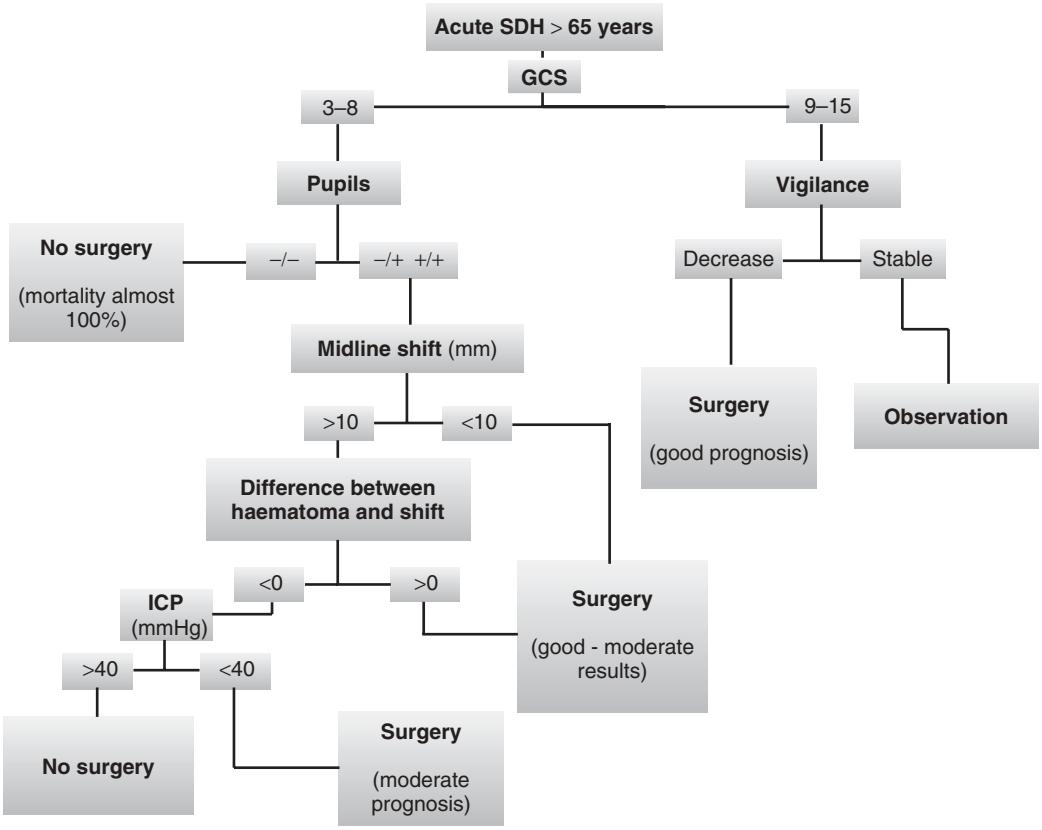

Figure 60.3 Acute subdural haematoma management algorithm, based on Petridis *et al*.[4] See the section on management of acute SDH for details.

linked to the extension of intracranial bleeding. In patients treated with anticoagulants and suffering from severe head injury, antagonism has to be started as soon as possible after admission. A specific early management protocol for patients exposed to intracranial haemorrhage might reduce the mortality rate.[11]

Association between mechanical cardiac valves and traumatic head injury is not unusual in the elderly population. There is no significant increase in vital risk if anticoagulants are temporarily stopped for 1–2 weeks. In contrast, mortality and morbidity in antiplatelet drug-treated patients are mainly related to a premorbid condition. In patients presenting with head injuries and acute SDH, prophylactic anticoagulation should be started 72 h after the trauma.[12]

Outcome

Increasing age is a strong independent factor in prognosis for severe traumatic brain injury, with a significant increase in poor outcome in patients older than 65 years of age. Among patients with acute SDH, there is a relationship between poor outcome and age, low GCS and signs of herniation, but it is not possible to predict death with certainty on the basis of old age and poor GCS.

Chronic subdural haematoma

Chronic SDH is a common but puzzling disease. This disease is fairly frequent in the very young but is found mainly in the elderly and those with prior brain atrophy. Although frequent, chronic SDH is treacherous condition: the elderly population with chronic SDH has a demonstrated increased risk of morbidity and mortality.[2,13] Chronic SDH is also a puzzling condition as the mechanism of constitution and expansion is still not fully understood. The presentation and pathophysiology of chronic SDH are different from those of acute SDH. For chronic SDH, neurological symptoms and brain dysfunction are purely the results of brain compression, as there is rarely a trauma severe enough to cause significant primary injury or initiating secondary injury. However, we must emphasize the *continuum* between acute and chronic SDH. Differentiating acute and chronic conditions is appropriate in a taxonomic approach, but SDH should be considered as a very dynamic process. The main characteristic of a chronic SDH is its resolution with sometimes little therapeutic intervention. This suggests that this condition may sometimes be asymptomatic throughout the population and undergo spontaneous resolution without treatment in a number of cases.

A stated above, chronic SDH is a common condition with increasing age, but also a mysterious condition. Indeed, the mechanism by which the initial clot becomes large enough to compress the underlying brain is not fully understood. Even stranger is the fact that resolution of chronic SDH occurs in most cases merely from a solitary drainage, leaving intact the membranes deemed to be the cause of the expanding nature of the chronic SDH.

Epidemiology

The mean age at diagnosis is 56–63 years and men outnumber women by 3:1. Although it is not exclusively a disease of old age, chronic SDH is much more common in the elderly. As the elderly population of the Western world has increased, chronic SDH has become a more frequent neurological problem. Its incidence in individuals younger than 65 years of age has been reported to be 3.4 per 100 000 people, whereas in those older than 65 years of age estimates range between 8 and 58 per 100 000.[14] Throughout the world, at present almost one in 10 people are over 60 years old, and by 2050 the figure will be higher than one in five. In 2009, individuals >65 years of age accounted for 39.5 million people in the USA and 85.1 million in Europe (12.8% and 17.3% of the respective populations). By 2030, the population older than 65 yeas is expected to double worldwide, and is projected to climb to 20% of the population in the USA and 25% in Europe. Based on the increase in the ageing population alone, the incidence of chronic SDH is expected to double worldwide in the next 25 years. This known increased risk has to be anticipated in terms of prevention, management and therapeutic intervention in order to lessen its effect on a fragile population, especially in terms of dependency.

Various conditions are prone to the development of chronic SDH. Brain atrophy is the most important predisposing factor as it provides a potential space for haematoma expansion. This explains the high mortality and morbidity of chronic SDH. Atrophy is a predictor of poor outcome after chronic SDH.[15,16] Haematoma thickness also tends to be larger in older patients. Major dehydration is a less commonly associated condition and is found concurrently in only 2% of patients. Fall is an important risk factor as it is related to dementia and brain atrophy. Hence the patient is trapped in a vicious circle: cognitive and gait impairment, fall, minor and repeated brain trauma, micro bleed, chronic SDH, brain function impairment, cognitive and gait decline, fall, . . . and so on. Other risk factors have been identified: alcohol abuse, seizures, CSF shunts, cardiovascular disease (hypertension, arteriosclerosis), thrombocytopenia, diabetes and coagulopathies including therapeutic anticoagulation. The number of patients who receive antiplatelet and/or anticoagulant drugs is increasing, especially in the aged population. In a recent paper, the use of antiplatelet and/or anticoagulant drugs was demonstrated to be over-represented among patients with non-traumatic chronic SDH compared with patients with a history of head trauma.[17] There was, however, no significant association between medication with antiplatelet and/or anticoagulant drugs and recurrence of chronic SDH. Considering the increased use of antiplatelet and anticoagulant drugs in modern cardiovascular and neurovascular medicine, attention should be drawn to the possible risks of intracranial bleeding complications and the benefit-to-risk ratio of these drugs has been addressed. However, in comparison with the powerful stroke prevention action of antiplatelet and anticoagulant drugs, the side effect of chronic SDH remains small.

Pathophysiology

Many chronic SDHs start out as acute subdural. The haematoma results from tearing of a bridging vein. The tendency for bridging veins to be disrupted in the subdural rather than the subarachnoid space is thought to be due to the lack of outer reinforcement of the bridging vein there. In the subdural space, the veins lack the support of the arachnoids' trabeculae and are thus more fragile. The initial SDH is small in most cases and, owing to the venous origin of the haematoma, is not usually associated with a sudden or steep increase in intracranial pressure. In addition, the wide sulci and the atrophic brain allow for dome enlargement before the onset of significant neurological symptoms. In acute SDH, displacement of the brain resulting in a midline shift >10 mm is usually associated with elevated ICP, often greater than 40 mmHg. In patients suffering from chronic SDH, however, normal pressure has been observed in the presence of a midline shift as large as 20 mm. Owing to the slow expansion of the haematoma, the period of spatial compensation of the haematoma is probably long enough to cause considerable distortion of the brain before there is a significant rise in intracranial pressure.

Membrane formation around the haematoma is a characteristic feature of chronic SDH. Such membranes are thought to be due to a non-specific inflammatory response of the highly vascular inner layer to the presence of blood products, fibrin and fibrin degradation products in the subdural cavity.[18] The avascular arachnoid has a much lower reaction potential than the inner dural layer in which blood evokes an inflammation response. Within days, fibroblasts invade the clot and form neomembranes on the inner (cortical) and outer (dural) surface. This is followed by in-growth of neocapillaries, enzymatic fibrinolysis and liquefaction of the blood clot. Fibrin degradation products are reincorporated into the new clots and inhibit haemostasis.[19] Whereas acute SDH shows a thick, reddish clot, chronic SDH usually produces a much darker brownish fluid similar to motor oil.

Secondary enlargement of chronic SDH is common. It has been hypothesized[20] that the membrane around the haematoma acts as an osmotic membrane, with CSF diffusing into the hyperosmotic haematoma. Repeated microhaemorrhage from the neocapillary network in the outer membrane or abnormally high vascular permeability are thought to be responsible for haematoma enlargement. Therefore, the course of enlargement is determined by the balance of plasma effusion and/or rebleeding from the neomembranes on the one hand and reabsorption of fluid on the other.

Clinical presentation

A subdural haematoma is considered chronic when it is discovered 3 weeks or more after the initiating injury. However, the trauma is minimal or even unrecognized in one-third of cases.[21]

The classic presentation of a post-traumatic chronic SDH includes two phases. The first phase is the traumatic event, which is usually minor. After its dissipation and a silent period of various lengths, the second phase begins with the onset of delayed clinical manifestations. The time elapsed between the first and second phases is deemed to represent the formation and maturation of haematoma membranes. The clinical manifestation usually consists of non-specific headaches, drowsiness or unsteadiness, decline in mental function, confusion and language or motor deficits. Focal deficits with hemiparesis and dysphasia may present in dominant hemisphere collection. From time to time, the patient may complain of recurrent symptoms like transient ischaemic attack, or they may develop varying degrees of coma or seizures, either focal or less often generalized. The three main complaints are gait disturbance or fall, mental disorientation and limb weakness.[22] Owing to the protean presentation of chronic SDH, the diagnosis is often unexpected prior to the imaging. Due to the progressive, subacute degree of neurological failure, the diagnosis of chronic SDH is difficult. In older patients, a slow decline within weeks or few months can be related to a chronic SDH. Coagulopathy and anticoagulant therapy may accelerate this presentation in many cases.

There are many other neurological conditions that yield very similar clinical presentations of a slow decline: stroke, tumour, hydrocephalus and primary neurodegenerative disorders represent differential diagnosis.

Investigation

CT scanning is the method of choice for investigation: scanning is easily accessible, quick, efficient and cheap. The CT scan shows the location, size and age of the SDH and also the alteration of the brain parenchyma. On a CT scan, subdural haematomas are classically described as delineated fluid collections that are crescent-shaped, with the concave surface away from the skull. They are fairly easily identified, located and measured in size.

The attenuation pattern of subdural blood changes over time. X-ray attenuation of a fresh clot is dependent on haemoglobin. Every acute blood collection with a haematocrit >23% has a higher density than the brain parenchyma: 80 Hounsfield units for the clot in comparison with 30 Hounsfield units for the normal brain. Therefore, the acute SDH is hyperdense with respect to the normal brain. This hyperdense pattern of the clot last only 1–3 days. After the acute phase, the SDH becomes less dense due to haemoglobin clearance and becomes more fluid due to inflammation, oedema and CSF diffusion. Between 4 days and 2 weeks, the subacute SDH is isodense with the brain parenchyma (~30 Hounsfield units). Between 2 weeks and 3 months, thanks to haemoglobin clearance and fluid formation, chronic SDH has a density slightly higher than that of water (~10 Hounsfield units), that is, a lower density than the brain, termed hypodense. Over 3 months, SDH either spontaneously resolves or turns into fluid collection, also known as hygroma, with a density almost identical with CSF (~0 Hounsfield units by definition). In most cases, the presentation of a mature chronic SDH has a mixed density with acute bleeding. The diagnosis of chronic SDH is fairly easy on CT imaging. However, subacute SDH is sometimes difficult to identify owing to its isodensity with the brain. In such cases, subtle signs of bleeding such as effacement of sulci or medial displacement of the junction between grey and white matter should be sought. It is important to delineate the underlying brain alteration. One should gauge the mass effect on the brain parenchyma: displacement and distortion of anatomical structures, midline shift, ventricles effacement or oedema. The underlying brain atrophy is difficult to identify in the early phase. The extent of atrophy is sometimes difficult to determine in preoperative CT scans, especially in the presence of midline shift and contralateral ventricular dilation. An example of bilateral chronic SDH is displayed in Figure 60.4.

Magnetic resonance imaging (MRI) is less often used to identify and manage chronic SDH. Although MRI is more efficient at analysing isodense haematoma and fluid, this examination is costly and time consuming. Haemosiderin, which is a constant feature of parenchymal haematomas, is rarely seen in chronic SDHs. The MRI signal of a chronic SDH is mainly defined by the concentration of methaemoglobin. However, this concentration is very dynamic due to dilution, absorption and/or degradation. In general, chronic SDH displayed more hyperintensity than normal brain in both T1 and T2 weighted MR images.[23,24] This technique is also useful for distinguishing chronic SDH from hygroma. A chronic SDH older than 30 days gives a low or isointense signal on T1 and a high

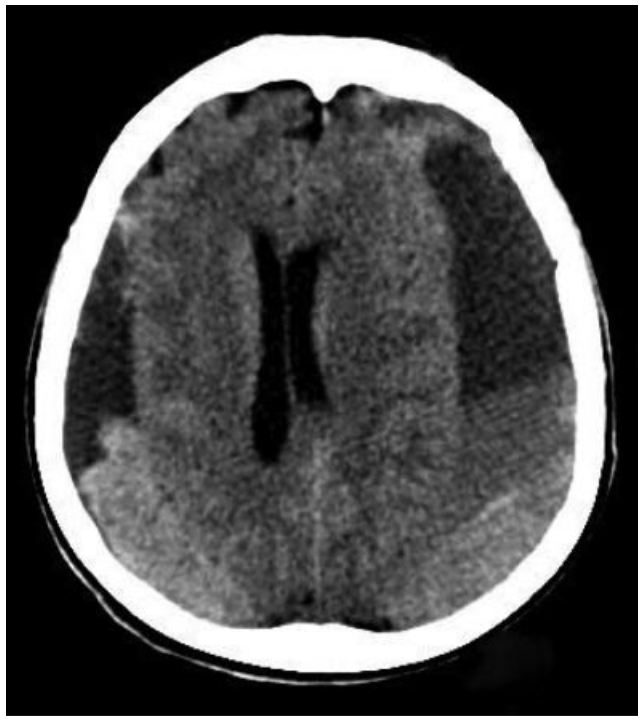

Figure 60.4 CT scan of a bilateral chronic subdural haematoma in an elderly patient with significant atrophy. On the left side, note the heterogeneous pattern of the SDH: chronic hypointense ventrally, acute hyperdense dorsally and subacute isodense in between.

signal on T2 weighted images which are similar to the CSF signal.

Angiograms are sometimes considered for non-traumatic, non-coagulopathy-associated acute SDHs as micro-arteriovenous malformation or aneurysms might produce acute bleeding in the subdural space. Out of the context of unexplained acute SDH, chronic SDH does not require an angiogram.

Management

As mentioned earlier, chronic SDH is an unusual disease: sometimes asymptomatic and resolving spontaneously without treatment or healing with little therapeutic intervention. Medical management is sometimes proposed, but most of the time a symptomatic chronic SDH is operated on and drained. However, the surgical procedure is prone to complications.

The *medical management* of chronic SDH is controversial. Non-operative measures, such as, hypertonic or hyperosmolar solutions and systemic glucocorticoids have been proposed to treat or more precisely to reverse the vicious circle of fibrinolysis in chronic SDH. Noticeably, the literature concerning these therapies is encouraging with favourable results but consists of small case series and very few clinical observations.[25] However, dexamethazone (e.g. 8 mg every 8 hours) should be in the armamentarium to heal a chronic pauci symptomatic chronic SDH.

The *surgical treatment* is the reference treatment. The neurosurgical evacuation of the haematoma results in a great improvement in neurological condition. Three techniques are most often used: twist-drill craniostomy, burr-hole craniostomy and craniotomy. Twist-drill craniostomy[26] consists in drilling a small hole of diameter <5 mm in the skull to drain the haematoma and if necessary insert a drain. This technique is very simple but does not permit any visual control of the intracranial procedure. Burr-hole craniostomy[15] involves a larger hole (5–30 mm) that allows the visual control of the dura and the cortex which can be coagulated prior to incision. This latter technique permits proper drain insertion, but does not result in the optimal drainage as membranes are intact. Craniotomy involves surgical opening of the skull. This is a much more aggressive technique with a large bone flap and direct access to the brain, the haematoma and the membranes. It allows substantial evacuation of the haematoma, rinsing and even membranectomy. Markwalder's review on chronic subdural haematoma was an important step in minimizing the invasiveness of the surgical treatment.[15] A meta-analysis[13] comparing all three techniques concluded that they have about the same mortality (2–4%). Craniotomy is associated with a much higher morbidity than is craniostomy (12.3 versus 3–4%) and recurrence with twist-drill craniostomy is much higher than with burr-hole craniostomy (33 versus 12.1%) and craniotomy (33 versus 10.8%). Burr-hole craniostomy, with evacuation via one or two burr-holes drilled over the site of the haematoma, is the most popular surgical technique worldwide. However, recurrence after the initial drainage procedure ranges from about 5 to 30%.[13] Whether a drain should be left in place after burr-hole craniostomy has been much debated until recently. A recent and well-performed randomized trial clearly found the benefit of postoperative drainage in the management of chronic subdural haematoma after burr-hole evacuation.[22] Recurrence occurred in 9% of the patients with drain and 24% for those treated with a single burr-hole without drain. At 6 months mortality was 8% in the drain group and 18% in the no-drain group, but medical and surgical complications were much the same between the groups.

Complications after surgical evacuation of a chronic SDH are not rare and potentially lethal. Because of old age and the frailty of most patients with the condition, an overall complication rate of 21% has been reported.[25] Wound infection, subdural empyema, tension pneumocephalus, seizures, brain contusion, subdural or epidural haematoma, intracerebral or intraventricular haemorrhage, catheter penetration of the brain and even death may occur after surgery. The mechanisms underlying this event remain unclear,

especially within the ventricular system. The need for a slow and gradual decompression of haematoma is essential. The recurrence of the haematoma is fairly frequent and can be significantly reduced by placing a drain after evacuation of the SDH. By means of an artificial neural network for outcome prediction of chronic SDH, various conditions have been identified as risk factors for postoperative recurrence: postoperative intracranial air, high-density haematomas and low Glasgow coma scale on admission. Other risk factors for recurrence include history of seizure, alcohol abuse and CSF shunts.[27] The role of antiplatelet and/or anticoagulant drugs in chronic SDH has also been examined in various studies. They failed to demonstrate an increased risk of recurrence of chronic SDH.[17] The only independent factor for recurrence seems to be bilateral chronic SDH.[28] However, it seems that the substitution of coagulation factors has to be considered.

Outcome

There is a clinical improvement when the subdural pressure is reduced to close to zero, which usually occurs after 20% of the collection has been removed. Patients who have high subdural fluid pressure tend to have more rapid brain expansion and clinical improvement than patients with low-pressure chronic SDH. Clinical improvement does not require complete resolution of the fluid collection. CT scans showed persistent fluid in 78% of cases at 10 days and 15% at 40 days.[15] A simple drainage procedure is sufficient to treat successfully almost 80% of patients and 90% with two procedures. Overall mortality with surgical treatment of chronic SDH is in between 5 and 10%.[13] Outcome is also related to the clinical condition at the time of treatment; worsening of neurological status following drainage occurs in 4% of cases.

Subdural hygroma

Subdural hygromas involve accumulation of CSF in the subdural space.[29] They are more common in men, usually located in the frontal region and may be uni- or bilateral. They usually occur after head injury, but have also been described after meningitis, craniotomy, shunt and venous thrombosis. They may also be spontaneous or a traumatic complication of arachnoid cysts. The development of hygroma into chronic SDH is not uncommon; however, the mechanism by which this transition occurs is not fully understood.

Pathophysiology

A trivial trauma can cause a separation of the dura–arachnoid interface, which is the basic requirement for the development of a subdural hygroma. If the brain shrinks due to brain atrophy, excessive dehydration or decreased intracranial pressure, fluid collection may develop by a passive effusion. The mechanism of formation of hygroma is probably a tear in the arachnoid membrane with resultant CSF leakage into the subdural compartment. Hygroma fluid contains prealbumin, which is also found in CSF but not in subdural haematomas. Hygromas may be under high pressure and may increase in size due to a possible flap-valve mechanism. The resulting mass effect exerts a pressure on the brain with the possibility of significant morbidity. Persistent traumatic hygroma usually results in haemorrhage into the subdural fluid owing to the tearing of bridging veins or bleeding from the neomembrane. Between the brownish 'motor oil' of a chronic SDH and the crystal clear fluid of hygroma, there is a variety of subdural collections, either blood tinged or xanthochromic under variable pressure regimens. Mild to severe ventricular dilations were observed in some patients. Ventricular dilation that occurs late after trauma when subdural hygromas reduce, probably does so by an *ex vacuum* compensatory effect. In these cases, the sulci and fissures are evident by localized or diffuse atrophy. However, not all ventricular dilations can be explained by an atrophic process. Some of them could be a result of disturbance in CSF absorption bridging subdural hygroma and external hydrocephalus.

Clinical presentation

There is no specific sign attributed to subdural hygroma, because its clinical aspects are overlapped by other traumatic lesions. The diagnosis of subdural hygroma almost always is discovered by evolution CT scan about 2 weeks after trauma; however, some studies have found subdural effusions as early as 24 h before hygroma formation. Many patients present without focal findings and there is no specific symptomatology attributed to hygromas. Complex hygromas usually present more acutely and require more urgent treatment. Elderly patients with marked age-related brain atrophy and a widened CSF space can cause confusion on differential diagnosis.

Investigation

On CT scan, the density of a hygroma is similar to that of CSF (~0 Hounsfield units by definition). MRI is more efficient in differentiating proper hygroma from late chronic SDH. CSF fluid has a specific MRI pattern with a low signal on T1 and a high signal on T2 weighted images. Residues of blood, especially methaemoglobin, can also be identified with MR techniques.[30] The mass effect of a subdural hygroma on the cortex has to be considered, as it might indicate a pressurized fluid collection.

Management

Since the majority of patients with a subdural hygroma do not show a mass effect, surgery is rarely required. Outcome is closely related to the primary head injury and not to the hygroma itself. The complexity of subdural hygroma depends on various factors, including the dynamics of absorption and expansion, duration of observation and indication of surgery. Among the variety of the primary head injury with respect to types and severity, subdural hygroma is a common epiphenomenon of head injury. Most hygromas resolve when the brain is well expanded. However, a few hygromas become chronic SDH. Asymptomatic hygromas do not require treatment. In rare instances, a hygroma may be large causing a mass effect on the brain and requires surgical treatment. Simple burr-hole drainage is then proposed.

Key points

- Acute SDH is a devastating disease in the elderly.
- Acute SDH mandates reversal of anticoagulation as soon as possible.
- Surgery has to be considered in the elderly according to a management algorithm.
- Every slow decline within weeks or a few months can be related to a chronic SDH.
- CT scan is the method of choice to show, measure and date chronic SDH.
- Evacuation of a chronic SDH with a burr-hole and drain improves 80% of patients.
- After surgery, the complication rate is 20% and the overall mortality is 10%.
- Antiplatelet and/or anticoagulant drugs increase the risk of non-traumatic chronic SDH.
- The powerful stroke prevention of antiplatelet and anticoagulant drugs renders chronic SDH a small side effect.

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CHAPTER 61

Epilepsy

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Introduction

Epilepsy is the third most common neurological diagnosis in old people after dementia and stroke. The peak ages of onset of epilepsy are in childhood and old age (Table 61.1).[1] About 25% of newly diagnosed patients and 23% of people with epilepsy in the community are over the age of 60 years. However, little epilepsy research has been undertaken in elderly subjects and there have been only three double-blind randomized trials of antiepileptic drugs (AEDs) in the elderly.[2] Epilepsy is defined as the tendency to recurrent seizures, excluding febrile convulsions. A single seizure is not considered as 'epilepsy', although studies have suggested that up to 75% of people go on to have a second seizure and in the elderly this may be as high as 90%.[3]

A seizure results from a paroxysmal abnormal synchronous electrical discharge in the brain. A diagnosis of epilepsy is not an endpoint diagnosis – it should automatically lead to investigations for classifying the type of seizure (compare making a diagnosis of jaundice) as epilepsy is the result of many diverse neurochemical, neuropathological and neurophysiological abnormalities. Epilepsy is a clinical diagnosis based on an eyewitness description of an episode. At least 10% of people with a diagnosis of 'epilepsy' do not have the disorder. One of the commonest misdiagnoses is reflex anoxic seizures. These occur when someone feels faint and is kept upright, a few muscle jerks occur and a diagnosis of an 'epileptic' seizure is made. As epilepsy has such serious consequences with regard to activities of daily living, in particular driving, it is a diagnosis which should not be made lightly. If there is doubt, it is better to await clear evidence. An electroencephalogram (EEG) does not make the diagnosis of epilepsy as many trivial abnormalities are often overinterpreted. An EEG simply helps classify the kind of epilepsy – localization-related or generalized.

Aetiology

In the majority of elderly patients who develop epilepsy, it will be presumed to be secondary to cerebrovascular disease (Table 61.2).[4] Although the majority of patients are worried that they have an underlying brain tumour, this is rare. Neurodegenerative diseases such as Alzheimer's disease account for a significant percentage of those developing epilepsy. With the advent of MRI scanning, it is likely that in a higher proportion of patients an aetiological factor will be found in a higher proportion of elderly patients.

Dementia

Epileptic seizures are common in demented patients, especially in the later stages of the disease. A study in Dundee suggested that 9% of patients had had an epileptic seizure; 92% of reported seizures were tonic–clonic. As complex partial seizures are generally more common than tonic–clonic seizures, this would suggest that many partial seizures probably go unrecognized. Patients developing epilepsy were significantly younger and more severely demented. On the whole, the epilepsy appeared to be reasonably well controlled.[5] Another study found that the mean onset of epilepsy was 6.5 years (range 2–15 years) after the onset of the dementia. There was a threefold increase in the incidence of epilepsy compared with a reference population.[6] A study of 446 autopsy-proven cases of Alzheimer's disease found that 17% were documented as having seizures during their lifetime. However, two-thirds of patients had less than three seizures, suggesting that on the whole the seizure disorder was mild.[7]

Cerebrovascular disease

Cerebrovascular disease is the commonest cause of seizures in the elderly. Cerebrovascular disease increases the risk of

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Table 61.1 Incidence of epilepsy at different ages.

Age (years)	Incidence
0–10	60:10^5
20–40	40:10^5
60–69	101:10^5
70–79	150:10^5
80–89	190:10^5

Reproduced from Tallis *et al.*[1] by permission of Oxford University Press.

Table 61.2 Aetiology of the seizure disorder in elderly people with epilepsy.

Cerebrovascular disease	30–42%
Tumour	2–14%
Dementia	2–14%
Toxic/metabolic	6–12%
Other	22–58%

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an epileptic seizure by a factor of 20 and is the commonest cause of seizures in the elderly. There is an increased risk of developing epilepsy in the first year after a cerebrovascular accident by a factor of 17 compared with the risk in age-matched patients in the general population.[8] The overall incidence of seizures after a cerebrovascular accident varies between 4.4 and 12.5%, depending on the population studied and the methods used. Studies looking at the risk factors for the subsequent development of epilepsy have suggested that patients with haemorrhagic strokes, embolic stroke, cortical lesions, hippocampal involvement or lesions involving more than one lobe are at greater risk of developing epilepsy. Early seizures within 2 weeks of a cerebrovascular accident (2–8%) are due to acute biochemical abnormalities, and late seizures (after 2 weeks) are secondary to chronic processes such as removal of inhibition and formation of new synaptic connections. Epileptic seizures in old age are often the first signs of cerebrovascular disease and therefore people presenting with a first seizure should be evaluated for risk factors for vascular disease as they have a 2.8–9 greater risk [95% confidence interval (CI) 2.45–3.40] of having a stroke within 5 years.[2,9] A post-ictal Todd's paresis is often misdiagnosed as a stroke recurrence and if the patient has a seizure with a weakness then this alternative diagnosis needs to be considered.

Diagnosis

The diagnosis of epilepsy is the same in elderly as in younger patients. It is a clinical diagnosis based on eyewitness description of the episodes. One of the major problems in diagnosing epilepsy in the elderly is that they may be unable to give a description of what is actually happening to them before or after an attack and, as they often live on their own, an episode may not have been witnessed. A classical tonic–clonic seizure is relatively easy to diagnose from eyewitness descriptions. Minor attacks such as absence or complex partial seizures are much more difficult to diagnose. Often they may consist of staring episodes where the person is not responsive for a few seconds. These can be followed by automatisms or confusion, often short-lived. An EEG is useful for the classification of seizure type. Only rarely can it be used to make a diagnosis, that is, if a seizure occurs while an EEG is being performed or specific diagnostic EEG changes occur. In addition, the post-ictal period can be longer in the elderly, lasting from hours to days, leading to the incorrect diagnosis of dementia.[10] In more than 50% of elderly patients who were finally diagnosed with epilepsy, epilepsy was not the initial suspected diagnosis.[11] In the elderly, after the first seizure the risk of recurrent seizures is very high, greater than 90%.[3] Suggestions have been made that elderly patients should be treated with AEDs after the first seizure.

Differential diagnosis

Transient ischaemic attacks (TIAs)

A TIA is a vascular event lasting less than 24 h. It tends to be associated with negative phenomena such as weakness or sensory loss. Conversely, epilepsy tends to have positive phenomena such as paraesthesias or jerking of a limb. However, at times it is difficult to differentiate simple partial seizures from TIAs. If consciousness is lost, it is very unlikely to be a TIA. It also has to be remembered that cerebrovascular disease is an important aetiological factor in the development of epilepsy.

Transient global amnesia

This is not an uncommon disorder occurring in later life, when a person has no memory for a significant period of between a few hours and a day or so. Eyewitnesses say that the person appeared normal and was able to perform complex tasks. On closer questioning, the person often was repeating the same questions such as 'what time is it?' A person tends to have only a single episode, so if repeated the diagnosis needs to be reconsidered. The symptoms are due to a defect in memory for events of the present and recent

past. During the episode, consciousness is retained and there is no impairment in intellectual functioning. Studies have suggested that there is no increase in risk factors for vascular disease and no subsequent increase in cerebrovascular disease. There is, however, an increased incidence of migraine. Transient global amnesia is an important diagnosis to make in that, unlike epilepsy, people in the UK with this condition, after reporting to the Driving Vehicle Licensing Authority (DVLA), are allowed to continue driving.

Cardiac arrhythmias

These are very important in the differential diagnosis of epilepsy in the elderly. If the brain is starved of oxygen, for whatever reason, a tonic–clonic seizure will result. Both tachy- and bradyarrhythmias can result in tonic–clonic seizures. Clues to the fact that the seizure may be a secondary phenomenon may be found in the prodrome. A history of feeling faint or palpitations should make a clinician suspect a cardiac cause for the episodes of loss of consciousness. A 24 h EEG with an ECG lead, videotelemetry and reveal devices can be useful in trying to differentiate between a cardiac and an epileptic episode. If the episode is cardiac in nature, the arrhythmia will begin before the abnormal electrical activity in the brain by a significant time lapse. It has to be remembered that during a seizure it is not uncommon for a cardiac arrhythmia to occur, but it will begin at about the same time as the abnormal electrical activity in the brain.

Syncope

If a person is kept upright during a vasovagal attack, it is not uncommon for a few myoclonic jerks to occur and in susceptible people a tonic–clonic seizure can result. The events leading up to the episode of loss of consciousness and also eyewitness descriptions are very important. The feeling of faintness, dizziness and the need to get fresh air preceding the episode make it likely that the episode was syncopal rather than epileptic in nature. The person is usually upright during the episode. They feel dizzy, queasy and giddy and often things recede or go black. Pallor is noted and often a cold perspiration. Nausea and vomiting occasionally accompany these symptoms. After falling to the ground, consciousness is regained very fast, and if the person lies down the episode can often be aborted. A few myoclonic jerks can occur, as can incontinence if the bladder is full. Micturition syncope, especially in men having to get up during the night, is a relatively common cause of loss of consciousness; so too is cough syncope. The elderly are more prone to syncope as they may have impaired cardiovascular reflexes or be on vasodilating drugs such as glyceryl trinitrate (GTN) or have carotid sinus hypersensitivity.

Psychogenic epileptic attacks

Psychogenic epileptic attacks are thought to be rare beginning in the elderly but are commonly misdiagnosed as people often have underlying organic problems.

Panic attacks

It is rare for these to present *de novo* in the elderly as usually there is a life-long history. The person feels that something is going to happen. He/she feels the need to take deep breaths, becomes dizzy and light-headed, develops paraesthesias in the limbs and around the mouth and the legs become heavy. Symptoms can be reproduced by getting the person to hyperventilate. The initial precipitant was often a faint and panic attacks develop subsequently because of a fear of a further episode.

Drop attacks

These are episodes of unknown aetiology where a middle-aged or older person, usually a woman, will suddenly drop to the ground. There is no preceding warning and consciousness is not lost. There is often bruising to face, hands and knees. After the episode, the person can get up immediately. The EEG is normal, even during a fall. There is no treatment.

Hypoglycaemia

Hypoglycaemia is a rare cause of tonic–clonic seizures. It obviously needs excluding in diabetic patients on treatment. Rarely an insulinoma can produce tonic–clonic seizures. Other metabolic causes such as hypocalcaemia can precipitate seizures.

Alcohol and drugs

Alcohol abuse and withdrawal can precipitate seizures and it is important to take an alcohol history, even in the elderly. Many drugs, particularly tricyclic antidepressants, antimalarials, phenothiazines and butyrophenones, lower the seizure threshold and can precipitate seizures. The withdrawal of benzodiazepines occasionally can produce seizures.

Sleep disorders

Seizures during sleep need to be differentiated from parasomnias, but usually epilepsy can be diagnosed by taking a good history from the patient and obtaining an eye-witness description of the episode. A REM (rapid eye movement) sleep behaviour disorder occurs when somebody

acts out their dreams. Periodic limb movement disorders are characterized by periodic movements occurring during non-REM sleep. Most commonly people dorsiflex their ankles and flex their knees and hips every 20–40 s and this can be associated, in about 30% of patients, with restless legs syndrome. Hypnic jerks are a normal phenomenon occurring in about 70% of the population and consist of brief myoclonic jerks at sleep onset.

Seizure classification

Epilepsy is classified in two ways. There is classification of the seizure itself (Table 61.3)[12] and then there is syndromic classification.[13] Epilepsy is divided into two main groups. The generalized epilepsies are when the abnormal electrical activity rises from both hemispheres together (generalized spike wave). Localization-related epilepsy is when the abnormal electrical activity arises in one place in the brain and then spreads.

Generalized epilepsies

The generalized epilepsies are divided into two broad categories, primary and secondary.

Primary generalized epilepsy is probably a channelopathy that manifests itself in various syndromes such as childhood absence epilepsy and juvenile myoclonic epilepsy. Various types of seizures can occur, such as absence seizures, myoclonic and tonic–clonic seizures in association with generalized spike wave (three per second) on the EEG. These syndromes tend to occur in people of normal intelligence and begin in childhood or early adult life, although occasionally new-onset cases have been seen in the elderly or the diagnosis has been missed. Minor seizures beginning for the first time in the elderly are not absence seizures or *petit mal*. They are likely to be complex partial seizures. Primary generalized epilepsy responds best to treatment with sodium valproate or lamotrigine or levetiracetam as second-line therapy. The outlook for total seizure control is excellent. The majority of children with childhood absence epilepsy will be seizure free and off treatment by adult life. Most patients with juvenile myoclonic epilepsy become seizure free but will relapse if treatment is stopped even if the patient is elderly. Many elderly people with a long-standing seizure disorder will never have had their epilepsy classified. In particular, the diagnosis of juvenile myoclonic epilepsy is commonly missed. Changing someone on to a more effective AED such as valproate can render them seizure free even in extreme old age.

Symptomatic *secondary generalized epilepsy* is more commonly seen in people with learning disabilities.

Table 61.3 Classification of seizures.[12]

- **I** *Partial seizures*
  - A Simple partial seizures
  - B Complex partial seizures
    - 1 With impairment of consciousness at onset
    - 2 Simple partial onset followed by impairment of consciousness
  - C Partial seizures evolving to generalized tonic–clonic convulsions
    - 1 Simple evolving to generalized tonic–clonic convulsion
    - 2 Complex evolving to generalized tonic–clonic convulsion (including those with simple partial onset)
- **II** *Generalized seizures*
  - A Absence seizures
    - 1 Typical absence seizures
    - 2 Atypical absence seizures
  - B Myoclonic seizures
  - C Clonic seizures
  - D Tonic seizures
  - E Tonic–clonic seizures
  - F Atonic seizures
- **III** *Unclassified seizures*

Localization-related epilepsy

In localization-related seizure disorders, the abnormal electrical activity begins in one area of the brain and spreads. The seizure manifestations depend on the site of onset of the abnormal electrical activity and the rate of involvement and spread to other areas of the brain. For example, abnormal electrical activity arising in the temporal lobe may begin with a feeling of fear or *déjà vu* or an abnormal taste or smell. This is a simple partial seizure, which is rarer in the elderly than younger patients with epilepsy.[14] As the abnormal electrical activity spreads, it involves more of the temporal lobe and consciousness is lost – a complex partial seizure. The person may be seen to stare or gulp or swallow or perform repetitive movements or automatisms. If the abnormal electrical activity spreads to the other side of the brain, a tonic–clonic seizure results. Therefore, tonic–clonic seizures occur in both generalized and localization-related epilepsies. This is the type of epilepsy that usually begins in late adult life. Tonic–clonic seizures are usually readily recognized as being due to epilepsy but are rare in the elderly (26%) compared with younger patients (65%).[14]

Investigations (Table 61.4)

EEG (Table 61.5)[15]

The diagnosis of epilepsy is based on an eyewitness description of a seizure, plus the exclusion of other causes. An EEG is useful in trying to classify the type of seizure disorder and occasionally in diagnosis if seizure activity is captured. Many patients without epilepsy will have minor

Table 61.4 Investigation of epilepsy in the elderly.

EEG	**Routine**
	Sleep deprivation
	24 h ambulatory
	Video telemetry
ECG	Routine
	24 h ambulatory
REVEAL device	
Basic haematology	
Urea and electrolytes	
Blood sugar	
Calcium	
CXR	
CT scan/MRI	

Table 61.5 Types of EEGs.

Routine EEG (20 min)
- To try to confirm the diagnosis of epilepsy
- Classification of epilepsy syndrome
- To determine presence/absence of photosensitivity

Sleep/sleep-deprived EEG (if original EEG is normal),
To help make diagnosis of epilepsy
To classify the seizure disorder

Ambulatory EEG
- Detection/quantification of generalized spike wave discharges

Video-EEG telemetry
- Diagnosis of undiagnosed paroxysmal attacks (need to occur at least weekly)
- Suitability for epilepsy surgery

abnormalities in the EEG, particularly in the elderly because of cerebrovascular disease. Between seizures, a person with epilepsy can have a normal EEG, so an EEG is not an appropriate tool to diagnose epilepsy. A referral to a cardiologist may be indicated. If an ordinary EEG is normal, a *sleep deprivation EEG*, performed after a night without sleep, can sometimes be helpful. *Ambulatory ECGs* and *videotelemetry* can be useful in the diagnosis of odd episodes of loss of consciousness. A 24 h ambulatory EEG is portable but only records from a few scalp electrodes. An ECG lead should be recorded at the same time. When the person feels an event coming on or it has happened, an event button is pressed. The episode can be reviewed for both the cardiac rhythm preceding and during the event and the EEG activity. However, it must be realized that epileptic episodes may be missed or misinterpreted because of the placement of electrodes or movement artefact. Videotelemetry is a more sophisticated monitoring technique that is only available at specialist neurological centres. A standard EEG and ECG are recorded at the same time as the patient is videoed. This means that the episode can be observed as well as looking at the EEG. Neither of these investigations is likely to be of value unless the patient is having at least weekly episodes.

ECG

A routine ECG can either demonstrate a cardiac arrhythmia or suggest that a patient may be prone to a brady- or tachyarrhythmia, for example, heart block or an supraventricular tachycardia (SVT). If cardiac causes are suspected, a 24 h ECG is mandatory. Occasionally a REVEAL device may be indicated.

CT scan/MRI

A form of imaging is valuable in trying to determine the aetiology of the seizure disorder, especially as neurosurgeons will consider operations on older patients. If seizures are focal in origin, an MRI scan is the most sensitive investigation to look for underlying pathological changes. A normal CT scan will exclude any major underlying pathology, although a small low-grade glioma may not be visible. A change in seizure frequency or the development of neurological signs is an indication for rescanning. Other investigations such as basic haematology, biochemistry and an ECG are usually performed. Various other investigations may be indicated, depending on the likely aetiology of the seizures.

Treatments

The aim of treatment is to suppress seizures totally with the lowest possible dose of one AED. This can be achieved in over 80% of elderly people developing epilepsy[16] and the majority are on monotherapy. The choice of drug depends on the type of seizure disorder and various factors such as other medical conditions and therapies. The elderly are also more prone to AED side effects and interactions partly because of concomitant diseases and medications. Long-term antiepileptic treatment also predisposes towards osteoporosis. It is estimated that AED treatment for over 5 years doubles the risk of osteoporotic fractures in the elderly.[17] In primary and symptomatic generalized epilepsy, the drug treatment of choice is sodium valproate, levetiracetam or lamotrigine. In people with localization-related epilepsy, all the first-line drugs are equally effective; they just differ in side effects. It is therefore advisable to choose a drug with a low side effect profile such as carbamazepine, sodium valproate, lamotrigine or levetiracetam. Barbiturates (phenobarbitone, mysoline) have little place in today's treatment of epilepsy. Phenytoin, although an effective drug, is difficult to use. Second-line therapies include gabapentin, topiramate, zonisamide, lacosamide and tiagabine. Clobazam can be useful for predictable

seizures or when they occur in clusters. A study looking at AED usage in the elderly showed that the mean dose of AED was lower than in younger patients. Even so, 27% of these patients felt that they had side effects from their medication.[18] Several studies have shown that a greater proportion of drugs such as phenytoin, sodium valproate and benzodiazepines are present in the free state in plasma in the elderly, which implies a higher brain concentration. There is an alteration in the half-life and clearance of the commonly used AEDs, suggesting reduced dosage requirements. Clinical studies have shown that lamotrigine and gabapentin are better tolerated than carbamazepine in the elderly but the difference disappears if carbamazepine (controlled release) is used and increased slowly.[19–21] The majority of clinical decisions about antiepileptic treatment in the elderly are based on data for younger patients' experience and principles of pharmacotherapy in the elderly.[2] A study of 622 patients showed that 64% of patients over the age of 60 years had to stop taking an AED because of side effects compared with 33% of younger adults.[22] Elderly patients are more sensitive to central and systemic side effects of AEDs, particularly cognitive side effects. If one of the commonly used monotherapy drugs fails to control seizures adequately then a referral to a neurologist or specialist epilepsy clinic may be helpful.

Antiepileptic drugs (Tables 61.6 and 61.7)

Phenobarbitone

Phenobarbitone is an effective AED but its use is accompanied by an unacceptably high incidence of behavioural problems and sedation. There are many new drugs that are just as effective, but produce a much lower incidence of side effects.

Primidone

Primidone is a compound that is converted in the body to phenobarbitone. It has an even higher incidence of side effects than phenobarbitone and should no longer be used.[22]

Phenytoin

Phenytoin is an effective AED but appears to have a higher side effect profile than some of the newer agents. It is a difficult drug to use because of its many interactions and saturable metabolism. Phenytoin has a narrow therapeutic range and non-linear pharmacokinetics, so small increases in dosage can precipitate toxicity. A comparative study of phenytoin and sodium valproate suggests that they are both equally effective in controlling seizures in the elderly, while having similar effects on cognitive function.[23]

Carbamazepine

Carbamazepine is one of the first-line drugs for the treatment of partial seizures. It can have a positive effect on behaviour. It is a hepatic microsomal enzyme inducer and therefore speeds up the metabolism of other drugs such as warfarin, phenytoin, phenobarbitone and lamotrigine, in addition to inducing its own metabolism. Its main side effect is a rash, which occurs in about 10% of people. If it is given in high dosages, people are likely to complain of double vision and drowsiness. If this occurs after a dosage increase, it is worth waiting for a week to see if symptoms resolve as hepatic enzyme induction occurs and blood levels fall. Maximum tolerated monotherapy dosages tend to be between 800 and 1200 mg per day. The retard formulation tends to be associated with a lower incidence of peak dose side effects.

Sodium valproate

Sodium valproate is the other first-line drug for localization-related epilepsies and the treatment of choice for the

Table 61.6 Antiepileptic drug summary: useful management pointers – treatment of localization-related epilepsies.

Carbamazepine
Benefits: a commonly used, very effective AED
Caution: Interactions with other drugs metabolized by cytochrome P450 including warfarin
Side effects. rash/Stevens–Johnson syndrome. Those at greatest risk are those who have had previous rash with phenytoin/phenobarbitone/lamotrigine or are of Han Chinese or Thai origin. Hyponatraemia. Low white-cell count. Osteomalacia
Contraindications: AV conduction abnormalities, bone-marrow depression

Oxcarbazepine/Eslicarbazepine
Similar to above. Lower incidence of sedation/rash. Possible increased incidence of hyponatraemia

Gabapentin
Benefits: no interactions. Excreted unchanged by the body. Effective in neuropathic pain
Caution: reduced dose in renal failure
Side effects: dizziness, peripheral oedema, weight gain

Pregabalin
Benefits: Related to gabapentin but more powerful. No interactions. Also licensed for generalized anxiety, neuropathic pain
Caution: reduced dose in renal failure
Side effects: weight gain, sedation, dizziness, peripheral oedema

Phenytoin
Benefits: once daily dosage, does not need titration
Caution: very easy to precipitate toxicity. Interactions with other drugs metabolized by cytochrome P450 including warfarin
Side effects: rash, gingival hypertrophy, hirsutism, ataxia, blood disorders, osteomalacia

Lacosamide
Little experience in the elderly
Contraindications: cardiac conduction problems
Side effects: nausea and vomiting, drowsiness, prolonged PR interval

Table 61.7 Antiepileptic drug summary: useful management pointers – treatment of localization-related and generalised epilepsies (i.e. broad-spectrum AEDs).

Valproate
Benefits: most effective AED for generalized epilepsies
Caution: encephalopathy, parkinsonism
Side effects: weight gain, thrombocytopenia, osteoporosis

Lamotrigine
Benefits: possibly the most effective AED for localization-related epilepsy
Caution: interaction with other AEDs
Side effects: rash, Stevens–Johnson syndrome, insomnia

Levetiracetam
Benefits: no interactions with other drugs
Caution: renal impairment
Side effects: irritability, depression

Topiramate
Benefits: Also effective as migraine prophylaxis
Caution: ensure adequate hydration
Side effects: cognitive impairment, mental slowing, paraesthesias, renal calculi, weight loss

Zonisamide
Benefits: once daily dosage
Caution: ensure adequate hydration
Side effects: irritability, weight loss, sedation, depression, cognitive impairment, renal calculi

Clobazam/Clonazepam (benzodiazepines)
Benefits: quick action, good at terminating seizures
Caution/contraindications: respiratory depression, sleep apnoea, neuromuscular respiratory weakness
Side effects: drowsiness, tolerance
Note: often used as a PRN medication

Phenobarbitone
Advantages: once daily
Side effects: sedation, rash, osteomalacia

generalized epilepsies. The main side effects of sodium valproate are weight gain, tremor and hair loss at higher doses. About 60 cases of acute fatal hepatic failure have been reported with valproate therapy, the majority being children under the age of 2 years with developmental delay. These problems should be differentiated from the benign elevation in liver enzymes that occurs in about 30% of patients treated with valproate. Parkinsonism with cognitive decline has been reported and was found in about 2% of the elderly receiving sodium valproate.[24] Sodium valproate can also predispose towards osteoporosis. The elderly may be slightly more at risk of a low platelet count compared with younger patients.

Gabapentin
Gabapentin is an AED that is structurally related to GABA. It is an effective AED in partial seizures but does not appear to work in absence seizures and may exacerbate some symptomatic generalized seizure disorders. It is also licensed for chronic pain. It has a low side effect profile. The main side effects reported are dizziness, drowsiness and light-headedness. Its benefits are its ease of use and lack of interaction with drugs including other AEDs, apart from a minor interaction with cimetidine. Gabapentin is excreted unchanged in the urine; therefore, doses do need to be reduced in renal failure. It has been evaluated after stroke in the elderly.[25]

Pregabalin
Pregabalin is structurally related to gabapentin. Clinical studies have shown it to be effective as add-on therapy in resistant partial seizures. It has not been evaluated in the elderly. It is also licensed for neuropathic pain and generalized anxiety. It is effective and well tolerated in the elderly. Pregabalin does not have any major interactions with other drugs and is excreted unchanged by the kidneys. Its main side effects are dizziness, somnolence and weight gain.

Lamotrigine
Lamotrigine is a broad-spectrum AED like sodium valproate and is active against both generalized and partial epilepsies. It is well tolerated with a low side effect profile. Its main problems are rash and interactions with other AEDs. This has meant that differing dosage schedules and maximum doses are used according to concomitant AEDs. Its half-life varies from 15 h when used in combination with enzyme inducers such as phenytoin or carbamazepine to 30 h when used as monotherapy and 72 h when combined with sodium valproate. Studies in elderly patients suggest that it is well tolerated[26] and often only low doses are needed to suppress seizures.

Topiramate
Topiramate appears to be an effective AED but does have a high side effect profile, including mental slowing and difficulties in concentration. Studies in the elderly showed it to be well tolerated and effective.[27] It can cause significant weight loss and there is a risk of renal calculi.

Clobazam
Clobazam is a 1,5-benzodiazapine specifically licensed for the treatment of epilepsy. It is used in a dose of between 10 and 30 mg at night. Its main problem is that, if used daily, tolerance tends to develop in 30–70% of people. It is very useful for predictable seizures or if seizures cluster. It can be used to terminate episodes of minor status.

Clonazepam

Clonazepam tends to be used for generalized epilepsies. Again it has the problem of tolerance and appears to be more sedative than clobazam.

Diazepam/midazolam

Rectal diazepam is of considerable value in terminating episodes of convulsive and non-convulsive status epilepticus. It can be used in the community and the need for hospital admission may be avoided. There is a video available from the manufacturers to teach carers in the use of rectal diazepam. A more acceptable alternative (although not licensed or evaluated in the elderly) is buccal midazolam (10 mg). It and rectal diazepam can be used to stop prolonged seizures or status epilepticus in the community.

Ethosuximide

Ethosuximide decreases absence and atypical absence seizures (generalized epilepsies). It is of no value in complex partial seizures and so has little use in the elderly.

Levetiracetam

Levetiracetam is a broad-spectrum AED. Subanalyses of studies have suggested that it is effective and well tolerated in the elderly.[28] Levetiracetam has a highly favourable pharmacokinetic profile in that it does not bind to protein and is excreted unchanged in the urine, so it should be used with caution in those with impaired renal function. A study in the elderly developing epilepsy after a cerebrovascular accident showed that it was effective and well tolerated.[29] Levetiracetam does not induce liver hepatic microsomal enzymes; it can be titrated rapidly and an effective dose can be initiated on starting therapy. About 7% of elderly people develop psychiatric problems or irritability.[28]

Tiagabine

Tiagabine is a GABA reuptake inhibitor that appears effective in people with complex partial seizures, particularly those who have responded to vigabatrin. At present it appears from clinical trials to have a lower side effect profile than vigabatrin and may provide a useful alternative to vigabatrin. It has not been evaluated in the elderly and is not commonly used.

Oxcarbazepine/eslicarbazepine

These are analogues of carbamazepine. They have advantages over the parent compound in that they appear to be less sedative with a significant lower incidence of side effects, including rash. Oxcarbazepine's main drawback is that there is an increased incidence of hyponatraemia compared with carbamazepine, so it may be of limited use in the elderly.[30] This particularly occurs in those who are on concomitant naturiuretic drugs. Oxcarbazepine and eslicarbazepine are effective against partial seizures. Eslicarbazepine is metabolized to oxcarbazepine.

Lacosamide

Lacosamide is a newly licensed AED for drug-resistant partial seizures. It appears to be well tolerated but there are no data in the elderly.

Antiepileptic drug level monitoring

Antiepileptic drug levels only need to be monitored in those patients who have continuing seizures in order to check compliance, which is one of the commonest reasons for therapy failure. Levels are much more difficult to interpret in the elderly because of an increase in the free state and the lack of a 'therapeutic' range in this age group. People are their own *in vivo* drug assays. If someone is seizure free, they are receiving the correct dosage of AED and no alterations in dose are indicated. If seizures continue without side effects, then the dose can be increased. If dose-related side effects occur, the dosage is too high. There is no bottom limit to the so-called therapeutic range and many people are able to tolerate plasma levels in excess of the 'upper limit'. Anticonvulsant levels occasionally are helpful for drugs such as phenytoin which have difficult pharmacokinetics and can give an idea of the scope for dose increments in someone with continuing seizures. Sodium valproate levels are of little value as there are wide fluctuations in measured concentrations throughout the day. Blood level monitoring is not needed for any of the recently licensed AEDs. A study in elderly patients suggested that the majority of samples taken for AED concentrations were taken for no specific reasons and there was a limited response to the results obtained.

Management of drug-resistant epilepsies

If seizures have failed to respond to a first-line AED, various questions need to be asked:

1. Is this epilepsy?
2. Is this the best AED for the seizure type?
3. Is it being given in an adequate dosage?
4. Is the person actually taking the drug?

If someone has genuinely failed to respond, alternative therapies need to be considered. If seizures are predictable, intermittent clobazam is a useful adjunctive therapy. If not, another drug needs to be added and the dosage increased until a response is obtained or side effects develop. If the second drug is ineffective, then it should be stopped before another therapy is considered. If it is effective, then the first drug gradually needs to be withdrawn, as the aim of treatment is someone seizure free on monotherapy.

Anticonvulsant withdrawal

The Medical Research Council (MRC) Antiepileptic Drug Withdrawal Study showed that in patients who have been seizure free, at least 40% were able successfully to withdraw from therapy. The longer the seizure-free period, the greater was the likelihood of success. Successful withdrawal was also associated with few seizures before becoming seizure free and the use of a single AED. Patients who had juvenile myoclonic had a >95% chance of relapse even if they had been seizure free for many years. This is the only group of people that needs to be on treatment for life.[31] Many elderly people would be able to stop AED therapy satisfactorily but are reluctant to decrease therapy because of the driving regulations. The DVLA in the UK suggests that a person does not drive while treatment is being reduced nor for 6 months after stopping treatment. If a person has a seizure on trying to come off therapy or afterwards, they need to inform the DVLA and may not drive for 1 year.

Status epilepticus

Status epilepticus is a major neurological and medical emergency associated with a high morbidity and mortality. It is defined as a condition in which epileptic activity persists for 30 min or more; this covers a wide spectrum of clinical symptoms and with a highly variable pathophysiological, anatomical and Aetiological basis. The elderly give rise to the largest number of status epilepticus cases per annum even though the incidence is higher in childhood. In patients with established epilepsy, tonic–clonic status epilepticus rarely occurs without warning. It is usually preceded by a phase in which seizures become increasingly frequent and severe. Urgent treatment with a benzodiazepine (such as clobazam, diazepam or buccal midazolam) or paraldehyde will often prevent the evolution into true status epilepticus. Once status epilepticus has developed, the patient needs to be admitted to hospital and i.v. lorazepam (4 mg bolus i.v.) or diazepam (10 mg at a rate of 2–5 mg min^{-1}) needs to be administered. If intravenous access is not possible, intramuscular (i.m.) or rectal paraldehyde is a useful alternative. If seizures continue, then an infusion of phenytoin (18 mg kg^{-1} at a rate of 50 mg min^{-1}, e.g. 1000 mg in about 20 min) with diazepam 10–20 mg over 5–10 min if not already given or phenobarbitone (10 mg kg^{-1} at a rate of 10 mg min^{-1}, e.g. 700 mg over 7 min) should be administered. If seizures continue for longer than 30–60 min, admission to an ITU is indicated, as treatment with a general anaesthetic using either propofol or thiopentone is needed. Anaesthesia should continue for 12–24 h after the last clinical or electrical seizure and then the dose should be tapered down/off. The clinical features of complex partial status are highly variable, reflecting the diverse underlying pathophysiology. Episodes frequently last for many hours. They are characterized by confusion that can fluctuate. They can often be precipitated by a tonic–clonic seizure, and can vary from a profound stupor to mild mental slowing. Characteristically, language may be sparse and answers to questions, although appropriate, are often delayed. There can also be motor manifestations and psychotic symptoms can occur. An EEG will be diagnostic.[32]

Driving

After a first seizure, in the UK the DVLA needs to be informed and usually driving will need to cease for 6 months. People with epilepsy who have been free of all types of seizures for 12 months or more may reapply for their licence. For those who continue to experience their seizures only during sleep, they may drive if that has been the only manifestation of their epilepsy for over 3 years.

Key points

- Epilepsy is the third most common neurological disorder in the elderly.
- It is important to make an accurate definite diagnosis.
- Epilepsy in the elderly is usually easy to treat.
- Use an appropriate AED (taking into consideration pre-existing disorders and medication) in the lowest possible dose.
- Long-term AED therapy predisposes toward osteoporosis.

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CHAPTER 62

Syncope and non-epileptic attacks[1]

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Introduction

Presentation with a 'collapse', 'blackout' or 'funny turn', with or without impairment of awareness and responsiveness, is common in older people and there is a wide differential diagnosis (Table 62.1). The commonest a etiologies are epileptic seizures, the various types of syncope and cerebral vascular disease. Epileptic seizures and cerebral vascular disease are discussed in other chapters; this chapter deals with syncope and some of the less common a etiologies, such as psychogenic non-epileptic attacks.

The information required to reach the correct diagnosis is usually contained within the history from the patient and from witnesses, and an adequate history will often obviate the need for extensive investigations. Difficulties arise most commonly when no witness account is available. When an attack has been witnessed, attempts should be made to contact a witness, even if he/she was a bystander not previously known to the patient. If a witness has not accompanied the patient to the consultation, a witness account can usually be obtained by making use of that important investigative tool, the telephone, and ringing the relative, friend, care assistant, shop assistant and so on, involved. General practitioners or ambulance personnel called to attend a patient who has collapsed can provide crucial diagnostic evidence, as they are in a position to interview witnesses while the features of the episode are fresh in their minds.

Diagnosis can sometimes be difficult. Pending clarification by the occurrence of further attacks, diagnostic uncertainties may persist even after specialist referral and investigation. It is usually better to accept this diagnostic uncertainty, explaining it to the patient and relatives, than to plunge for a specific diagnosis which may be incorrect and lead to inappropriate treatment and management. In particular, problems arise when non-epileptic attacks are labelled as epileptic. The patient then has to come to terms with an erroneous diagnosis to which significant stigma is still attached, and receives unnecessary antiepileptic drug treatment, possibly with adverse effects.

[1]This chapter is as in the Fourth Edition.

Syncope

Syncope can be defined as loss of consciousness due to transient impairment in blood flow to the brain. The term 'presyncope' can be used to describe symptoms of impending syncope. It is impaired flow to the brainstem and thalamus that is most likely to result in loss of consciousness, and thus adequacy of flow in the posterior (vertebrobasilar) circulation usually determines whether syncope will occur. The impairment in blood flow can occur for a variety of reasons, and it is important to recognize this since the different causes of syncope have differing symptoms and signs. A classification of syncope is given in Table 62.2. The incidence of the different causes of syncope changes with age. In the older patients, areflexic syncope, cardiac syncope and carotid sinus syndrome become increasingly frequent. It is a common problem, accounting for 0.77% of A&E department attendances, with admission rates increasing with age (Sun *et al*., 2004). A specialist syncope and falls service will improve the diagnosis and outcome (Kenny *et al*., 2002).

Mechanisms underlying syncope

A sudden fall in blood pressure and syncope can occur due to the following:

1 'Reflex syncope', when there is a reflex response of an intact autonomic nervous system to a trigger (e.g. vasovagal syncope, carotid sinus syndrome).

2 'Areflexic (paralytic) syncope', when an erect posture is adopted and there is postural hypotension due to a dysfunctional autonomic nervous system (e.g. autonomic neuropathy).

3 'Cardiac syncope', when there is a sudden reduction in cardiac output due to a cardiac disorder (e.g. bradyarrhythmia, tachyarrhythmia).

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 62.1 Differential diagnosis of blackouts and funny turns.

Syncope
Epilepsy
Transient ischaemic attacks
Panic attacks
Hyperventilation attacks
Other psychogenic non-epileptic attacks ('non-epileptic attack disorder')
Sleep phenomena
Hypoglycaemia
Migraine
Transient global amnesia
Cataplexy
Paroxysmal movement disorders
Paroxysmal symptoms in multiple sclerosis

Table 62.2 Classification of syncope.

Reflex	Vasovagal	Psychological (fear, trauma, pain)
	Carotid sinus	Low venous pressure (standing, haemorrhage)
	Micturition	Anoxia
	IXth and Xth cranial nerve disease	Neck pressure
	Oculocardiac	Micturition
		Glossopharyngeal neuralgia
		Neck tumours
		Ocular pressure (children)
Areflexic	Autonomic neuropathy	Upright posture
	Spinal cord disease	Upright posture
	Drugs	Upright posture
	Old age	Upright posture
Cardiac	Dysrhythmias	Exertion
	Ventricular outflow obstruction	
Respiratory		Coughing
		Trumpeting
		Weight lifting
		Hyperventilation
Cerebrovascular	Vertebrobasilar TIAs	

Syncope can also occur due to transiently reduced perfusion of the brain in 'respiratory syncope', when there is a transient increase in intrathoracic and intracranial pressure (e.g. cough syncope). Finally, a transient reduction in perfusion of the brainstem may also occur in cerebrovascular disease and occasionally present as syncope, for example, vertebrobasilar transient ischaemic attacks (TIAs). In elderly patients, there may be a combination of these mechanisms.

In reflex syncope a fall in blood pressure occurs due to (1) bradycardia and a reduced cardiac output (cardioinhibitory response), (2) vasodilatation in muscle and a reduced peripheral resistance (vasodepressor response), or (3) a combination of these mechanisms (mixed response) (Barcroft *et al*., 1944; Brigden *et al*., 1950). In vasovagal syncope, these responses can be distinguished by tilt testing, and in the elderly vasodepressor responses are much more frequent than in younger patients (Galetta *et al*., 2004). Recognition of this is important as insertion of a cardiac pacemaker is not likely to prevent attacks in patients with vasodepressor responses. In vasovagal syncope there is also reflex vasoconstriction in skin, causing pallor and reflex sweating. The trigger for these reflex responses is usually either 'psychological' (e.g. a response to fear, sight of trauma, pain) (Roddie, 1977) or low venous pressure detected by mechanoreceptors in the great veins and heart (e.g. prolonged standing, haemorrhage) (Abboud, 1989). Anoxia can be a trigger, and it is important in the context of anaesthesia and air travel (Sharpey-Schafer, 1956; Bourne, 1957). Non-massive pulmonary embolism may present as syncope, probably by triggering a vasovagal reflex (Castelli *et al*., 2003). In the carotid sinus syndrome syncope is thought to be triggered by activation of a 'hypersensitive' carotid sinus, and can be provoked by carotid sinus massage; again cardioinhibitory, vasodepressor and mixed responses occur. In micturition syncope, the trigger is the sudden loss of the pressor stimulus of a distended bladder (Taylor, 1963), occurring usually when the patient has got up to micturate at night, the skin is vasodilated, and the upright posture has just been assumed (contrary to common belief, 'straining' is not an important factor).

In areflexic syncope, the loss of the baroreceptor reflexes that normally keep the blood pressure stable despite changes in posture can occur for a wide variety of causes. These include autonomic neuropathy (in diabetes, Shy–Drager syndrome, Guillain–Barré syndrome, etc.) and spinal cord disease (in particular, traumatic cervical cord lesions) (Bannister, 1988). The baroreceptor responses tend to become more 'sluggish' in the elderly, causing an increased tendency to postural syncope with age. This can be exacerbated by a large range of medications, by dehydration, and by some conditions affecting the central nervous system (e.g. Parkinson's disease). Caird *et al*. (1973) found a postural fall in blood pressure of more than 20 mmHg in about 30% of a large elderly population, and a fall of more than 40 mmHg in 10%. Drugs implicated included ganglion blockers, diuretics, phenothiazines, antihistamines, antidepressants, benzodiazepines, barbiturates and antiparkinsonian drugs. Davidson *et al*. (1989) emphasized the role of drugs given for cardiovascular disease in causing syncope, in particular, nitrates, β-blockers and nifedipine. Donepezil may increase the risk of syncope. Orthostatic hypotension and syncope are common in the elderly following haemodialysis.

Cardiac syncope occurs in association with complete heart block (Stokes–Adams attacks), but also with other severe bradyarrhythmias, asystole, and paroxysmal

tachyarrhythmias (e.g. ventricular tachycardia). The commonest underlying condition is sinoatrial node dysfunction (sick sinus syndrome), with intermittent sinus arrest or sinus node exit block. If it is associated with atrioventricular block, paroxysmal tachycardia may also occur (tachy–brady syndrome). In the older patient, the arrhythmias will occur most commonly in the context of ischaemic heart disease. Cardiac syncope also occurs with ventricular outflow tract obstruction due to aortic stenosis or hypertrophic cardiomyopathy and may be associated with exertion.

A number of different mechanisms contribute to respiratory syncope (Sharpey-Schafer, 1953; McIntosh *et al*., 1956; De Maria *et al*., 1984). The rise in intrathoracic pressure associated with coughing, playing a wind instrument, weight lifting, or performing the Valsalva manoeuvre will be associated with a decrease in venous return to the heart, reduced cardiac output and fall in blood pressure. With cough syncope, which can occur after just one or several paroxysms of coughing, this will be only a brief response. Two additional mechanisms are of probable importance. First, the very high intrathoracic pressure transient is transmitted via the carotid artery to the baroreceptors, causing a more prolonged reflex fall in blood pressure. Second, the very high pressure transients are also transmitted via the venous system to the intracranial cavity, reducing cerebral perfusion pressure. Yet another mechanism is likely to contribute to syncope associated with hyperventilation; the fall in carbon dioxide partial pressure causes vasodilatation in muscle and reduced peripheral resistance.

Vertebrobasilar ischaemia may occasionally present as syncope, but there will usually be additional neurological symptoms. The underlying a etiology might either be embolic or related to critical changes in flow distal to atheromatous disease. With the latter the symptoms may be related to changes in posture.

Clinical manifestations of syncope

The usual image of a syncopal attack is of a subject feeling dizzy, going pale, falling with loss of awareness and then recovering rapidly within about 30 s. This sequence of events certainly occurs, but the variety of other manifestations of syncope of different types needs to be emphasized. The motor manifestations are particularly prone to cause diagnostic error and will be discussed first, followed by the other clinical features. In the elderly, presentation may be with a history of falls or drop attacks with no recall of loss of consciousness (Kenny *et al*., 2001).

Motor manifestations

A detailed study of vasovagal syncope in normal young volunteers led to important insights into the variety of clinical manifestations of syncope, which is relevant to the differential diagnosis of blackouts at any age. Lempert *et al*. (1994) induced vasovagal syncope in 56 of 59 volunteer medical students, by asking them to hyperventilate while squatting, and then to stand up performing the Valsalva manoeuvre. They carefully documented the manifestations with video recording. It was only a minority of subjects that lay still after falling, 90% having some asynchronous myoclonic jerks of the limbs. In a few, the jerks were quite vigorous for several seconds, such that the attack might be mistaken for a generalized clonic seizure. Some displayed other motor activity, such as limb-posturing, head-turning, complex movements, eye deviation and eyelid flicker, that might be misinterpreted as manifestations of partial epileptic seizures. Vocalization was frequent.

Similar findings of a very high frequency of myoclonic movements in syncope have also been reported in cardiac syncope (Aminoff *et al*., 1988). The opportunity to make these observations of the features of cardiac syncope has arisen with patients with recurrent ventricular arrhythmias treated with implantation of an automatic defibrillator, in whom syncope has been deliberately induced by induction of the arrhythmia to test the defibrillator. Simultaneous electroencephalogram (EEG) recording has shown no evidence of associated epileptiform activity. The variety of clinical manifestations of syncopal attacks has also been documented in attacks induced by use of a tilt table (Passman *et al*., 2003).

In vasovagal and cardiac syncope, therefore, the classic image of the patient falling, lying still for some seconds and then coming round is unusual, and much more often there are jerks and other motor manifestations. In these types of syncope it can be argued that the fall in blood pressure was very sudden and marked, and that this may have predisposed to the myoclonus. There is anecdotal evidence that the patient who faints, and who is propped up on falling rather than falling flat on the ground, is more likely to have myoclonic movements, presumably associated with a more prolonged and severe fall in blood pressure, and rarely the hypoxia may provoke an epileptic seizure. It may be that myoclonic movements are less common in patients with areflexic syncope and postural hypotension, in whom the presyncopal symptoms will often permit preventive measures, the fall in blood pressure is less catastrophic and the blood pressure will be immediately restored once they have fallen.

Other clinical features

The various trigger factors for the different types of syncope have been described in the preceeding text, and their importance will be discussed further in the section on diagnosis.

Warning symptoms, before loss of awareness, are common with reflex and areflexic syncope, but are absent in some patients (or not recalled). The symptoms of lightheadedness, dizziness and blurring of vision are familiar to most people on standing up from a hot bath too suddenly.

Additionally, there may be nausea, 'hot and cold' feelings, feelings of depersonalization or distance from the surroundings and buzzing in the ears. In the Lempert *et al*. (1994) study, described earlier, the students often described having had visual and auditory disturbances. Palpitations, dyspnoea and chest pain may occur (Graham and Kenny, 2001). Warning symptoms in cardiac syncope are less frequent and can consist just of a brief premonition as well as better-defined dizziness. A history of palpitations is usually sought, but positive responses are often difficult to interpret and negative responses are not diagnostically useful.

Marked pallor and clamminess are prominent features of vasovagal syncope due to the reflex vasoconstriction in skin and reflex sweating. In contrast, patients with areflexic syncope and postural hypotension may have relatively little colour change in association with their attacks, there is no sweating and the skin remains warm. Patients with cardiac syncope become pale owing to the marked reduction in cardiac output, and sometimes there is subsequent flushing when the output is restored (but this sequence is not sufficiently consistent or specific to be diagnostically very helpful).

If the opportunity arises to feel the pulse early in vasovagal and other causes of reflex syncope, it will be weak and there will be a reflex bradycardia. In contrast, in areflexic syncope there will be no change in heart rate. In cardiac syncope the heart rhythm changes could, of course, be diagnostic, but it is rare for a chance to arise to feel the pulse in an attack.

Not all syncopal attacks are associated with complete loss of either responsiveness or awareness. In the Lempert *et al*. (1994) study, 13 of the 56 subjects had a fall associated with only partial loss of awareness, and sometimes with confused behaviour that might be mistaken for a partial epileptic seizure. These phenomena are also well recognized in patients with postural hypotension and areflexic syncope.

Incontinence may occur with syncope of any type, and is not useful in differential diagnosis. Tongue biting is extremely rare, but has been reported as a consequence of the fall.

Syncopal attacks of any type are necessarily brief, with responsiveness returning in less than a minute and often much sooner. Marked reduction of cerebral perfusion for significantly longer periods would clearly result in ischaemic brain damage or death. Patients with reflex and with areflexic syncope usually recover very rapidly without confusion once supine, unless there has been a complicating factor such as head injury. Even patients with cardiac syncope and a transient severe reduction in cerebral perfusion recover rapidly. Following ventricular tachycardia or ventricular fibrillation, Aminoff *et al*. (1988) described recovery of consciousness within 20 s of restoration of the circulation, and subsequent confusion lasted no more than 30 s.

Diagnosis and investigation of syncope

The diagnosis of 'blackouts' is critically dependent on adequate patient and witness accounts of the attacks. In diagnosing syncope correctly, emphasis should be placed on potential trigger factors and the short duration of attacks. Thus, areflexic syncope is likely when there has been a clear relationship between the attacks and changes in posture, irrespective of a description of 'some jerking', other motor features, incontinence and injury in some attacks. Vasovagal attacks and other causes of reflex syncope are likely when potentially syncopal attacks have been associated with characteristic trigger factors and much less likely if they have not, in which case cardiac syncope should be seriously considered. The presence of underlying cardiac disease increases the probability of a cardiac cause. Cough syncope should be considered in patients with chronic obstructive pulmonary disease, emphysema and chronic cough, and an adequate witness account should be obtained, since some patients fail to recall the bout of coughing that triggers an attack. Syncope as a manifestation of cerebral vascular disease is unlikely in the absence of additional symptoms suggestive of posterior circulation transient ischaemic attacks.

In the last 15 years, increasing use has been made of tilt testing to obtain evidence to support a suspected diagnosis of vasovagal syncope and to investigate the underlying mechanisms (Grubb *et al*., 1991; Smith *et al*., 1994; Patel *et al*., 1993; Sutton *et al*., 1992). It has proved to be safe in the elderly (Gieroba *et al*., 2004; Galetta *et al*., 2004). The proportion of positive tilt tests is increased following the administration of glyceryl trinitrate. One of the difficulties in interpretation of the results, however, is the occurrence of positive tests in a significant minority of control subjects, which limits the positive predictive value. Nevertheless, provocation of a habitual attack is diagnostically very suggestive.

The work of Kenny has suggested that carotid sinus syndrome is a common cause of syncope in the elderly, and is not just confined to those with a history of fainting, following neck movement when wearing a collar (Kenny *et al*., 2001). Other groups have also reported a high incidence of syncope provoked by carotid sinus massage in patients with otherwise unexplained syncope (Freitas *et al*., 2004; Kumar *et al*., 2003). Carotid sinus massage appears to carry a very low risk of complications, despite potential underlying atheroma, but should not be carried out if there is a carotid bruit unless ultrasound examination has excluded severe carotid stenosis (Richardson *et al*., 2002).

When cardiac syncope is suspected, routine 12 lead electrocardiogram (ECG) recording will occasionally

demonstrate an arrhythmia, or abnormalities that predispose to arrhythmias. Twenty-four-hour ECG tapes can be diagnostic if an attack is recorded, but the yield of diagnostic recordings is very small unless the attacks are very frequent. Moreover, interpretation of the significance of asymptomatic rhythm disturbances can be difficult. In an older population, minor asymptomatic cardiac dysrhythmias are common and may be an incidental finding unrelated to a patient's attacks. When cardiac syncope is suspected, specialist cardiac referral will usually be indicated for further assessment, non-invasive investigation, and intracardiac electrophysiology in selected cases. In the last few years, implantable loop recorders have emerged as important tools in the diagnosis of cardiac syncope, permitting recordings of cardiac rhythm during attacks, even when the attacks are infrequent (Solano *et al*., 2004; Armstrong *et al*., 2003). The yield of positive recordings is greater in an elderly population (Brignole *et al*., 2005). Although the recorders are expensive, they can be cost-effective as there is a relatively high chance of capturing an attack and answering the clinical question (Krahn *et al*., 2003).

In areflexic syncope, the diagnosis is likely to be supported by finding a postural fall in blood pressure on examination that may or may not be symptomatic. The size of fall that is clinically significant varies between patients. A fall of at least 20 mmHg is usually defined as abnormal, but in some patients a fall of 10 mmHg is symptomatic, whereas in others with a higher supine blood pressure a fall of 40 mmHg might be asymptomatic. The blood pressure should be measured supine, immediately after standing and after standing for 1–2 min. Failure of the baroreceptor reflex responses can be confirmed by observing the heart rate changes in response to the Valsalva manoeuvre, standing and deep breathing.

There are a number of features of syncope that can cause diagnostic confusion with epileptic seizures. The jerky myoclonic movements might be interpreted as a generalized tonic–clonic seizure, but in the context of syncope these movements are brief, usually lasting only a few seconds and no more than 10 s. Other motor manifestations, a warning feeling of depersonalization, auditory and visual hallucinations and confused behaviour risk being misinterpreted as features of partial epileptic seizures. Pallor and clamminess are important features of vasovagal syncope but are not specific and such autonomic manifestations can occur in some partial epileptic seizures. Misdiagnosis of syncopal attacks as epilepsy can have tragic consequences when they are due to potentially fatal, but treatable, cardiac arrhythmias. Although most patients will have one type of attack, epilepsy and syncope can coexist. Rarely, patients have been described in whom an epileptic seizure has been triggered by a syncopal event and, conversely, significant cardiac arrhythmias (and potentially syncope) can occasionally be induced by epileptic seizures.

When a confident clinical diagnosis of syncope has been made, the temptation to request an EEG 'just in case it's epilepsy' must be resisted. If EEGs are done in a population of patients in which the prevalence of epilepsy is very low, then they have a very low positive predictive value (Scottish Intercollegiate Guidelines Network, 2003). Even if epileptiform abnormalities are found, the patient may still be more likely to have had a syncopal than epileptic attack. A request for EEG should be reserved for cases in which there is diagnostic uncertainty, and in which it is felt that epilepsy is a reasonably likely diagnostic possibility. It should be remembered that note should only be taken of definite epileptiform features and that non-specific slow-wave abnormalities are not diagnostically helpful.

Although the differentiation of syncope and epilepsy can be difficult, syncope is less likely to be confused with the other attack disorders listed in Table 62.1, which have characteristic clinical features or tend to cause attacks that are more prolonged.

Management of syncope

Vasovagal syncope is usually managed by avoiding provocative factors, and only a small proportion of patients need other interventions; many pharmacological treatments have been advocated, but are of no or uncertain efficacy, and pacemaker insertion may be ineffective (Brignole, 2003; Kaufmann and Freeman 2004; Connolly *et al*., 2003). Tilt training has been suggested, but is poorly tolerated and of uncertain benefit. In carotid sinus syncope the role of drug treatment is again uncertain; insertion of a cardiac pacemaker may need to be considered, if there is a significant cardioinhibitory component to the response to carotid sinus massage (Brignole, 2003; Healey *et al*., 2004). Surgical denervation of the carotid sinus is a possibility in severe cases. Micturition syncope can usually be avoided by micturating sitting down. Cardiac syncope requires appropriate specialist treatment with antiarrhythmic medication, pacing or insertion of an implantable defibrillator as appropriate; timely and effective treatment may be life saving. In cough syncope, treatment has to be directed at the underlying chest condition.

In older patients with syncope, areflexic syncope with postural hypotension is a common management challenge. Attention should first be directed to factors that may be causing or exacerbating the problem. The patient's medication should be reviewed, but it is not always possible to discontinue relevant drugs. For instance, in Parkinson's disease the effect of dopaminergic drugs in aggravating a postural fall in blood pressure may have to be balanced against their beneficial therapeutic effects. Treatable conditions such as Addison's disease should be excluded. Factors causing vasodilatation should be avoided, such as high

temperatures, marked exertion and alcohol. Small, frequent meals should be eaten rather than large meals. Dehydration should be avoided. When sitting up or standing, the changes in posture should be made slowly and reversed temporarily if postural symptoms supervene. Crossing the legs, tensing the calf muscles and abdominal compression can sometimes transiently ameliorate postural symptoms (Wieling *et al*., 1993).

Elastic compression stockings can make a significant contribution, although patients may need help in putting them on and they are difficult to tolerate in the summer. Sleeping with slight head-up tilt may help, possibly by expanding plasma volume, but a tilt of more than about 10° is difficult to tolerate. Chronic exposure to low blood pressure seems to improve cerebral autoregulation, so patients should be encouraged to remain as active as possible.

If these measures are not adequate in controlling symptoms of postural hypotension, drug treatment may be commenced. Most drugs are used without their licence and benefits may be limited. Fludrocortisone 100–200μg at night is usually commenced first and causes salt and water retention (and potentially hypokalaemia). Ephedrine, a sympathomimetic, can be added (15 mg t.i.d., increasing if necessary to 30 mg t.i.d.). Higher doses may cause tremor, tachycardia and agitation. A number of other drugs, including midodrine, have been used (Jankovic *et al*., 1993; Hoeldtke and Streeten, 1993; Mathias *et al*., 1986). With drug treatment supine hypertension is a risk. Pacing does not help (Sahul *et al*., 2004).

In an elderly population, the risks of serious injury and complications from falls are very high. It is important that the patient with syncope recognizes these risks, and understands the need to take precautions to avoid syncopal attacks, if at all possible.

Other non-epileptic attack disorders

Panic attacks and hyperventilation attacks

The clinical diagnosis of panic attacks in the context of an anxiety syndrome is usually straightforward, but fear and anxiety can of course be features of partial epileptic seizures. Treatment is directed toward the underlying anxiety disorder.

Hyperventilation may or may not be a component of panic attacks and, conversely, hyperventilation attacks may or may not be associated with panic. Classically, hyperventilation is associated with dizziness, paraesthesia in the hands and around the mouth and a paradoxical feeling of breathlessness. Feelings of unreality or depersonalization can occur, and may lead to a misdiagnosis of partial epileptic seizures, particularly when there is impaired consciousness, tetany or tremor. The hyperventilation can be subtle and not always obvious, even to an experienced witness. The paraesthesia and tetany are probably related to a reduction of extracellular ionized calcium induced by the respiratory alkalosis. The cerebral symptoms are ascribed to reduction of cerebral blood flow, and are associated with EEG slowing (Gotoh *et al*., 1965). Occasionally, loss of consciousness occurs in hyperventilation attacks, and this may be due to syncope caused by vasodilatation in muscle. It has been reported, however, that loss of consciousness can also occur without a fall in blood pressure, and it has been suggested that this is due to the severity of cerebral vasoconstriction (Naschitz *et al*., 1997). In the diagnosis of hyperventilation attacks, an attempt to induce symptoms by hyperventilation in the clinic or laboratory can be useful. Attacks may be aborted by rebreathing ('paper bag treatment'). Training in breath control and anxiety management by physiotherapists and/or clinical psychologists is indicated when the attacks are troublesome.

Psychogenic non-epileptic attacks

Psychogenic non-epileptic attacks ('non-epileptic attack disorder', pseudoseizures, functional seizures) present for the first time most frequently in teenage or young adult females, but there is increasing recognition that they also present in elderly patients. They are a common diagnosis in elderly patients undergoing assessment with long-term EEG and video monitoring in specialist epilepsy units (Kellinghaus *et al*., 2004). A significant number of patients with psychogenic non-epileptic seizures are misdiagnosed, in particular, as having epilepsy, and are treated inappropriately. Between 6 and 15% of patients investigated for apparently uncontrolled epileptic seizures have psychogenic non-epileptic seizures. When attacks persist despite treatment, a diagnosis of epilepsy should always be reviewed, and some patients with misdiagnosed psychogenic non-epileptic attacks will be identified. The correct identification of pseudostatus epilepticus is also very important.

A wide range of psychiatric labels have been attached to different patients with psychogenic non-epileptic attacks, in particular, conversion disorder and somatization disorder, but also anxiety, depression, post-traumatic stress disorder, episodic dyscontrol, and malingering. This suggests a variety of often ill-understood underlying mechanisms. With the exception of malingering, which is a very rare cause of an attack disorder, the attacks appear to occur without the conscious mediation of the patient. Often the attacks occur without any apparent trigger. One exception is episodic dyscontrol, in which rage attacks are triggered by irksome events and control of temper is inappropriately lost. In making a diagnosis of psychogenic attacks, it is usually important to take into account the 'whole picture' and not just one aspect of the patient's problems. As with other attack disorders, the diagnosis is critically dependent on adequate descriptions of the attacks but even with video recording, this may not, by itself, provide adequate

information. In a study in which neurologists attempted to make a diagnosis of epileptic or non-epileptic attacks on the basis of video recordings alone, they were correct in only 71% of epileptic seizures and in 73% of psychogenic non-epileptic seizures (King *et al*., 1982). In addition, account needs to be taken of the timing and circumstances of attacks, the detailed past medical and psychiatric history, current psychiatric, neurological and other symptoms and examination findings, bearing in mind that psychiatric symptoms are common in patients with epilepsy as well as in those with non-epileptic attacks. Other factors may be interictal and ictal EEG, the relationship of attacks to medication and measurements of serum prolactin.

The attacks tend to fall clinically into two main groups, those in which the patient collapses with impaired or absent responsiveness and little movement, and those with prominent motor activity (Meierkord *et al*., 1991). Betts and Boden (1992a) suggested an additional category of 'abreactive' attacks with hyperventilation, stiffening, breath-holding, gasping, incoordinate jerking and pelvic thrusting, and sometimes screaming, spitting and retching. In non-epileptic seizures, injury and incontinence are not uncommon, but tongue biting and cyanosis are very rare. In generalized tonic–clonic epileptic seizures, limb movements are in-phase, whereas in nonepileptic seizures with generalized limb movements they are usually out-of-phase (Gates *et al*., 1985). Some frontal lobe epileptic seizures can, however, also be associated with brief prominent out-of-phase limb movements (e.g. bicycling movements). Some attacks are easy to diagnose. For instance, episodes of collapse and unresponsiveness that are prolonged (e.g. 30 min) are most unlikely to be epileptic. Attacks with wild movements of all limbs and some degree of retained responsiveness are also unlikely to be epileptic. However, other attacks can be difficult to classify and require specialist referral.

Long-term video and EEG monitoring and the recording of attacks will usually, but not always, lead to a diagnosis. They are expensive. Even when attacks are relatively infrequent they can be worthwhile, as patients with psychogenic non-epileptic seizures tend to have more attacks than expected during monitoring. Indeed, short-term video EEG recordings on outpatients have been shown to have a high diagnostic yield when combined with suggestion that an attack will be provoked by hyperventilation or photic stimulation (McGonigal *et al*., 2004). The absence of epileptiform abnormalities during an attack does not exclude epilepsy, as many simple partial and rare complex partial seizures are not associated with scalp EEG changes. Prolactin level measurements have only a limited role. About 20 min after a generalized tonic–clonic seizure there is usually a marked rise in serum prolactin above 1000 mUl^{-1}, which is not seen in psychogenic non-epileptic seizures, but can occur following syncope (Trimble, 1978). The rise should be confirmed by measuring a baseline level or the level at least 1 h after the seizure. In practice, however, it is unusual to have much diagnostic difficulty with attacks that might be generalized tonic–clonic epileptic seizures and, with the more difficult diagnosis of attacks that might be partial seizures, the rise in serum prolactin is less marked and reliable. A rise above 500 mUl^{-1} is often seen after complex partial seizures, but not after simple partial seizures (Dana-Haeri *et al*., 1983; Laxer *et al*., 1985). However, such rises have also been reported following psychogenic non-epileptic seizures (Alving, 1998).

Between 10 and 30% of patients with psychogenic non-epileptic seizures also have epilepsy, and sometimes there is an inverse relationship between the frequency of the epileptic and non-epileptic attacks. In managing such patients, it is obviously necessary to distinguish clearly between the types of attack.

The first step in the management of psychogenic non-epileptic seizures is to explain the diagnosis clearly to the patient and his/her family. If the label of epilepsy has previously been attached, it is made clear that this is being removed (except in those with both types of attack). It is explained that a diagnosis of non-epileptic attack disorder is a positive diagnosis, that it is quite common and that the mechanisms underlying the attacks are sometimes not well understood. It is important that there is no hint of a suggestion that the attacks are being 'put on', and it should be made clear that this is not the case (except in the very rare malingerer). Further management will involve withdrawal of antiepileptic drugs, counselling from informed clinicians, nurse specialists or clinical psychologists and treatment of any associated depression or anxiety. It will usually be important to involve the whole family in the treatment programme. If the attacks are diagnosed early and any precipitating issues are dealt with, then the prognosis is good (Betts and Boden, 1992b). In the older patient with a long history of attacks, however, the prognosis for cessation of the attacks will be poor, and management will be aimed at helping the patient cope with them.

Sleep phenomena, hypoglycaemia, migraine, transient global amnesia, cataplexy, paroxysmal movement disorders and paroxysmal symptoms in multiple sclerosis

It is beyond the scope of this chapter to describe these remaining disorders in detail.

Episodic events during sleep can be due to normal physiological phenomena (e.g. hypnic jerks, periodic movements) and sleep disorders (e.g. myoclonus, restless legs syndrome, non-REM and REM parasomnias, sleep apnoea) as well as due to partial or generalized epileptic seizures. Periodic movements become increasingly frequent with age and are very common in an elderly population. They may disturb the sleep of the patient as well as that of the partner. They occur at a regular interval of 10–60 s and

usually consist of transient flexion movements of one or both legs lasting a few seconds. The restless legs syndrome also becomes more frequent with age and is associated with periodic movements of sleep. REM parasomnias occur characteristically in elderly males, last up to a few minutes and involve thrashing about and calling out in response to vivid dreams. Injury to a partner in the same bed is a risk. They can be confused with frontal lobe seizures and may respond to clonazepam.

Hypoglycaemia can cause a variety of manifestations. Attacks usually begin with autonomic disturbances such as sweating, palpitations, nausea and hunger. Symptoms related to cerebral dysfunction may then ensue, including paraesthesia, visual disturbance, weakness, tremor, dizziness, confusion and aphasia, as well as coma and epileptic seizures. Sometimes there are bizarre prolonged episodes of altered behaviour that might suggest a fugue state or partial status epilepticus. Most attacks occur in the context of diabetes, liver disease, alcohol abuse or in clear relationship to meals (reactive hypoglycaemia). Insulin-secreting tumours are very rare, and often diagnosed late.

The focal sensory, motor and psychic symptoms that can occur in migraine attacks may be mistaken as epileptic phenomena or ascribed to transient ischaemic attacks. The duration of migrainous symptoms tends to be longer (usually between 5 and 60 min) than the duration of epileptic symptoms (usually between a few seconds and 2 min). Associated headache, photophobia, nausea and vomiting will usually make a diagnosis of migraine clear. The loss of consciousness that can occur in vertebrobasilar migraine can cause diagnostic difficulty.

The diagnosis of transient global amnesia is usually immediately apparent from the history if a witness account is available to describe the profound amnesia (retrograde and anterograde) lasting usually between one and a few hours. There is often repetitive questioning with failure to recall the replies. The cause of the attacks remains uncertain and there is no specific treatment. It is important to distinguish them from prolonged postictal confusional states with amnesia that may follow partial epileptic seizures, and from ictal amnesia.

Cataplexy, paroxysmal movement disorders and paroxysmal symptoms in multiple sclerosis are unlikely to present for the first time in older patients. In all these conditions there is no impairment of consciousness, and responsiveness is only transiently impaired in cataplexy due to the transient weakness.

Key points

- In attack disorders a detailed account from the patient and witnesses is often crucial in reaching an accurate diagnosis.
- Motor manifestations lasting a few seconds (jerks, twitches, posturing) are common in syncopal attacks.
- Cardiac syncope, carotid sinus syndrome and areflexic syncope (with postural hypotension) become increasingly common in the elderly.
- Carotid sinus massage, tilt testing and cardiac loop recorders are playing an increasing role in the differential diagnosis of syncope.
- Psychogenic non-epileptic (functional) seizures can occur in older as well as younger patients, and are commonly misdiagnosed.

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CHAPTER 63

Parkinson's disease

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. Despite progress in understanding the neurochemical mechanisms, the exact cause of PD remains undetermined. The main pathological findings are loss of neurons in the substantia nigra and a profound depletion of dopamine in areas of projection pathways from the substantia nigra as in the striatum. In addition, a protein, α-synuclein, bound to ubiquitin accumulates in damaged neurons and contributes to form Lewy bodies, another hallmark of the disease found in cells of the substantia nigra and other brain areas. Several genetic factors, in particular about 10 gene mutations, have been identified in familial cases of PD, but they are observed mainly in early-onset PD and are infrequently involved in late-onset PD.

The prevalence of PD is ~1% in subjects aged over 65 years. The median age at diagnosis is 60 years, so less than about 40% of cases begin after age 60 years. Usually late-onset PD is defined by first symptoms occurring after the age of 60 years. Hence very late-onset PD, beginning after the age of 75 years, is not frequently observed. The incidence of PD rises with age until 80 years, but seems to decrease in the ninth decade. The mean duration of the disease from diagnosis to death is 15 years. Therefore, owing to age factors and referral bias, most PD patients seen in geriatric settings have a longstanding PD with impaired independence of other complications.

Risk factors for PD have been extensively studied. The existence of a family history of PD is found in 6–10% of cases. Weak associations have been found between PD and head injuries, rural living, obesity and exposure to herbicides or pesticides. Male gender is a controversial risk factor, depending on the population studied. Cigarette smoking and coffee consumption seem to be protective factors.

Signs and symptoms of very late-onset Parkinson's disease

Many symptoms can be caused by PD or other parkinsonian syndromes. Some of them are motor symptoms such as tremor, difficulties in moving, writing and walking, falls and changes in gait and posture. Others are non-motor symptoms such as bradyphrenia (slowness of mental function), depression, memory problems and dementia, constipation, bladder dysfunction and autonomic dysfunction (gastrointestinal, sexual, cardiovascular). Physical examination shows extrapyramidal signs which can suggest PD to the geriatrician (Table 63.1).

PD usually starts in an insidious manner and progresses slowly. Cardinal extrapyramidal signs do not appear at the same time and tremor can precede bradykinesia and rigidity for several months or years. PD signs are usually asymmetric or even unilateral at the beginning and become bilateral and/or symmetrical as the disease progresses.

Other signs are frequent in PD, especially as the disease progresses. *Abnormal posture* with flexion of limbs and trunk is observed when standing, and walking shows a decrease in step length and height and reduced swing of the arms. *Neuropsychiatric symptoms* are dominated by anxiety and depressive syndrome. Anxiety disorders encountered in PD are mainly generalized anxiety disorder and obsessive–compulsive disorder. Major depression episodes are frequent in PD and about 50% of patients might be affected during the course of the disease. The diagnosis of depression is often difficult because symptoms such as fatigue, sleep disorders and lack of interest may be encountered in PD in the absence of overt depression. *Cognitive symptoms* might be encountered is PD patients, but cognitive impairment (defined by an abnormally low performance in cognitive testing) is never a sign of early PD and is observed in PD only after several years of evolution (PD-related dementia).

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 63.1 Cardinal signs of Parkinson's disease.

Sign	Characteristics in PD	Conditions other than PD that should be considered
Tremor	At rest, 4–6 s^{-1}, asymmetric at the beginning, regular, increased by emotion, decreased by posture	Postural tremor: essential tremor, hyperthyroidism, drug-induced tremor, exaggerated physiological tremor, dystonia tremor Intentional tremor: cerebellar disorders
Bradykinesia and akinesia	Slowness and/or poverty of movements and speech, loss of facial expressions	Depression, dementia, hypothyroidism, drug-induced (sedatives), encephalopathy, parkinsonism other than PD
Rigidity	Found on passive movements, asymmetric at the beginning, lead-pipe type at examination	Pyramidal rigidity: abnormalities of reflexes and other neurological signs Oppositional rigidity: not permanent Extrapyramidal rigidity other than PD: axial or symmetrical at the beginning

Autonomic disorders are dominated by orthostatic hypotension and constipation. *Orthostatic hypotension*, frequently found in PD, is directly related to autonomic dysfunction and is often worsened by antiparkinsonian drugs. Orthostatic hypotension is often asymptomatic but can cause discomfort or fainting syncope. Orthostatic hypotension is defined by a decrease in systolic blood pressure by 20 mmHg (or diastolic BP by 10 mmHg) within 3 min following the passage from supine to standing. Repeated search of orthostatic hypotension is a part of the monitoring of any parkinsonism patient. *Constipation* is found in about 50% of PD patients and is related to bowel motility impairment, sphincter dysfunction and poor physical activity. Autonomic symptoms also include *sweating*, *drooping*, *sexual dysfunction* and *urinary symptoms*, such as urinary frequency, urgency and dysuria, whose links with PD can be established after having rejected the role of urinary infection, bladder or prostate diseases and/or anticholinergic drugs.

Differential diagnosis of Parkinson's disease

Tremor

PD may begin with isolated tremor. Other causes of tremor are listed in Table 63.1. Intention tremor which is increased by voluntary movement orients towards cerebellar diseases, and also other components of cerebellar syndrome (dysmetria, hypotonia, dysdiadokinesia, dysarthria) if present.

Postural tremor is increased by maintaining posture. Hyperthyroidism is easily recognized by other signs and blood determination of thyroid-stimulating hormone (TSH). Essential tremor is the main differential diagnosis. Family history of tremor and involvement of the head and voice are very suggestive of essential tremor. In difficult cases, brain single-photon emission computed tomography (SPECT) using a transporter of dopamine, ioflupane (DaTSCAN), shows a normal pattern in essential tremor and abnormalities in PD and other parkinsonian syndromes (except neuroleptic-induced parkinsonism). Drugs that might induce tremor include amiodarone, lithium, bronchodilators, metoclopropamide, neuroleptics, valproate and theophylline.

Extrapyramidal syndromes other than Parkinson's disease

Extrapyramidal syndromes can be observed in several conditions other than idiopathic PD. Especially in very late-onset parkinsonism, the relative frequency of extrapyramidal syndromes other than PD is greater than in early-onset parkinsonism, accounting for 20–40% of new parkinsonism cases in the elderly. The main causes of extrapyramidal syndrome are given in Table 63.2. In most cases, medical history and physical examination allow their identification. Parkinsonian syndrome other than PD responds poorly to L-dopa. This can be recognized by medical history if the patient was given L-dopa. In difficult cases, the response to L-dopa can also be clinically assessed (Box 63.1).

Drug-induced parkinsonism is very frequent in older patients. Neuroleptics, including those used as antiemetics, are the major cause of drug-induced parkinsonism. New antipsychotics (i.e. atypical antipsychotics, such as risperidone, olanzapine and quetiapine) also provoke parkinsonism even if this adverse effect in less frequent than with classical neuroleptics. Some other drugs infrequently induce parkinsonism, such as certain calcium channel blockers (cinnarizine, flunarizine), valproate and amiodarone. Cases with fluoxetine and other serotonin reuptake inhibitors have also been reported, but evidence is poor. Risk factors for drug-induced parkinsonism are advanced age and female gender. In about 50% of cases, extrapyramidal signs occurs within the first month after starting the drug, but might appear later.

Box 63.1 Response to L-dopa.

Response to L-dopa is sometimes useful to differentiate PD from other extrapyramidal syndromes. This is not formally a diagnosis test for PD but rather an indicator of dopaminergic response. If the patient has been previously treated with L-dopa for several weeks or longer, medical history helps assess the response to L-dopa. If the patient has not been treated before, this response can be assessed by administering to a fasting patient 150–250 mg of L-dopa associated with a dopa decarboxylase inhibitor. Tremor, rigidity and akinesia of members should be assessed every 30 min for 2–3 h. L-Dopa is not considered to improve non-motor symptoms or signs, and also posture and gait.

Extrapyramidal signs are usually bilateral and symmetrical. They comprise akinesia, bradykinesia and rigidity, but tremor is very unusual. By contrast, tardive dyskinesia, another movement disorder, is frequently associated in persons with neuroleptic-induced parkinsonism; it comprises involuntary movements of the lips, tongue and mouth, but could also involve other parts of the body. When the offending drug is stopped, signs of parkinsonism often alleviate, but this occur very slowly, over periods as long as several weeks or months. In about 20% of the patients, some extrapyramidal signs persist, which suggests that these people had PD or another neurodegenerative parkinsonism that was precipitated by the drug challenge. Tardive dyskinesia is often permanent in many patients, even after stopping the drug. There is no satisfactory treatment for drug-induced parkinsonism. Stopping the drug responsible is the best option and in elderly patients this is often possible since neuroleptics are mainly used to control behavioural complications of dementia, a condition for which they are ineffective. In elderly patients with severe psychosis, the switch from classical neuroleptic to low-dose atypical antipsychotic drugs should be tried. Anticholinergic drugs which are used in younger psychiatric patients treated with neuroleptics should be avoided in the elderly because they often induce delirium and other adverse effects. Prevention of drug-induced parkinsonism is a crucial issue in geriatric care and can be achieved by avoiding prescribing neuroleptics in elderly patients, especially in those with dementia.

Lewy body dementia and *Alzheimer's disease*, which are two frequent diseases causing dementia in older people, could be responsible for extrapyramidal syndrome. Lewy body dementia is strongly related to PD, since the two diseases share some physiopathological processes such as cellular Lewy bodies and α-synuclein metabolism abnormalities. Lewy body dementia is characterized by (i) cognitive dysfunction fulfilling the criteria of dementia, with insidious

Table 63.2 Causes of extrapyramidal syndrome other than Parkinson's disease.

Causes of extrapyramidal syndrome	Characteristics
Frequently observed as very late-onset parkinsonism	
Drug-induced parkinsonism	Exposure to neuroleptics (or other drugs) before the onset of parkinsonism. Dyskinesia is frequent. No tremor. Ioflurane SPECT normal pattern
Lewy body dementia	Dementia occurring a few months before or after the onset of parkinsonism, hallucinations, severe adverse reactions to neuroleptics
Alzheimer's disease	Parkinsonism is infrequent in Alzheimer's disease and is observed at moderate or severe stages. Hippocampal atrophy on MRI. Ioflurane SPECT normal pattern
Progressive supranuclear palsy	Postural instability and repeated falls occurring early in the course of the disease, axial rigidity, limitation of vertical gaze, neck dystonia, impaired saccades on ocular electrophysiology. No tremor. MRI: midbrain atrophy
Cerebrovascular disease	Parkinsonism associated with several cerebral infarctions on MRI and worsening of parkinsonism signs after infarctions. Usually with multilacunar state, pseudobulbar syndrome, emotional lability, pyramidal signs and/or vascular dementia
Normal pressure hydrocephalus	Gait disturbances, urinary incontinence, cognitive slowness. Cerebral imaging: marked enlargement of brain ventricles not explained by brain atrophy
Very rarely observed as very late-onset parkinsonism	
Multiple systemic atrophy	Severe dysautonomia (orthostatic hypotension, urinary disorder, sexual dysfunction, gastrointestinal symptoms) early in the course of parkinsonism. Pyramidal or cerebellar syndrome
Corticobasal degeneration	Dystonia, myoclonus and sensory disorders, foreign hand syndrome
Huntington's disease	Chorea, familial cases
Wilson's disease	Liver disease, complex neurological signs including parkinsonism, psychiatric symptoms, familial cases, Kayser–Fleischer ring around the iris
Miscellaneous	Toxic, post-encephalitis, repeated skull trauma

onset and progressive evolution, and (ii) association with one or several of the following features: hallucinations, extrapyramidal syndrome, fluctuation course, falls and poor tolerance to neuroleptics. The extrapyramidal syndrome might be present at the diagnosis of Lewy body dementia or might occur as the disease progresses. In some cases, the extrapyramidal syndrome might precede the onset of cognitive dysfunction for several months and often the diagnosis of PD is first considered; the occurrence of dementia in the few months after the diagnosis of extrapyramidal syndrome leads to the identification of Lewy body dementia. By contrast, PD-related dementia occurs in advanced stages of PD, after progression for several years. About 15% of patients with Alzheimer's disease are reported to experience extrapyramidal syndrome. Usually, extrapyramidal signs are mild and are recognized by physical examination. In many cases, the extrapyramidal syndrome might result from actual or past exposure to neuroleptics, which should be searched for carefully by interviewing patients, proxies, physicians and pharmacists. Extrapyramidal signs could also be observed in neuroleptic-free Alzheimer's disease patients. In these cases, the diagnosis of Lewy body dementia should also be considered. SPECT imaging of the brain using dopamine receptor radioligand helps to distinguish Alzheimer's disease from Lewy body dementia. The presence of extrapyramidal signs at the diagnosis of Alzheimer's disease is a reliable predictor of a more rapid decline.

Progressive supranuclear palsy is a neurodegenerative disorder which is frequently misdiagnosed as PD. The disease is characterized by an extrapyramidal syndrome associated with complex eye movement dysfunction. Tremor is infrequent and rigidity predominates at the spine. Posture and gait abnormalities are frequent at the early stage and lead to repeated falls, also favoured by attention and visual problems. Eye movement problems comprise the inability to shift the gaze downwards voluntarily, impaired saccades and difficulty in controlling the eyelids. Motor symptoms are unresponsive to L-dopa. As the disease progresses, changes in personality, dementia and swallowing problems are common. A typical pattern of MRI imaging has been described in progressive supranuclear palsy and relates to midbrain atrophy (Figure 63.1). Ocular electrophysiology also helps in recognizing supranuclear palsy and the disease.

Cerebrovascular diseases could also provoke extrapyramidal syndrome. This can be observed in patients with several brain infarctions, mainly a multilacunar status, in association with subcortical dementia and a pseudobulbar state. Posture and gait abnormalities are frequent and also swallowing problems. Tremor is infrequent and response to L-dopa is poor. The onset or the worsening of extrapyramidal signs within 1 month after a stroke strongly supports the diagnosis of cerebrovascular parkinsonism. Cerebral MRI documents vascular lesions of the brain as multiple lacunae and/or severe leukoaraiosis.

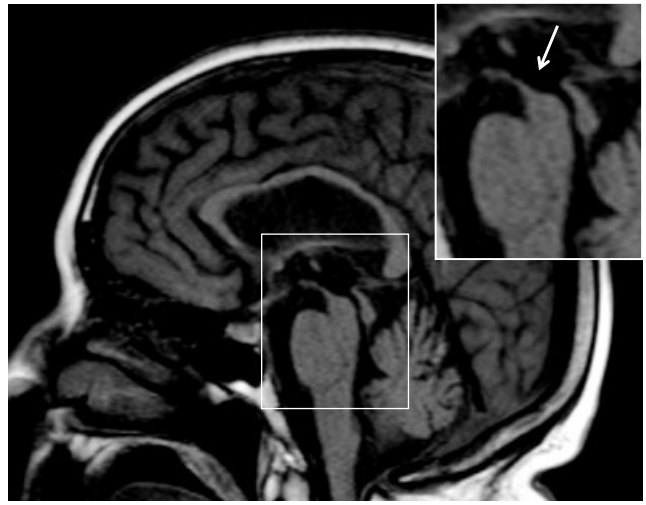

Figure 63.1 MRI showing convex aspect of the midbrain, indicating atrophy (arrow) typically observed in progressive supranuclear palsy (the normal midbrain aspect is concave).

Normal pressure hydrocephalus is a rare condition characterized by gait disturbance, dementia and urinary incontinence. Gait abnormalities could mimic those observed in PD with short steps, shuffling, slowness, stooped trunk and lower limb flexion, but there is no tremor or rigidity. Cerebral imaging shows marked enlargement of ventricles contrasting with the absence of cortical atrophy and small sulci and also periventricular high signals in the T2 sequence.

Other extrapyramidal syndromes are very infrequently observed in elderly people (Table 63.2).

To diagnose PD appropriately in an older individual, it is important to consider all other causes of parkinsonism and to examine whether criteria for PD are fulfilled (Table 63.3). In some cases, the diagnosis remains uncertain and follow-up usually clarifies it with the onset of new signs and symptoms.

Advanced Parkinson's disease

After 10–15 years of progression, PD is usually responsible for severe disability. Motor impairment could be major and alters several activities of daily living. Akinesia is often severe, whereas tremor and rigidity are less marked. The face is expressionless. Freezing problems are frequent. Posture and gait abnormalities are major and many patients experience repeated falls and fractures. Many patients are wheelchair bound. Patients often experience insomnia, pain, sweats, orthostatic hypotension, dysphagia, dysarthria, drooling of saliva, urinary

Table 63.3 Diagnosis criteria for Parkinson's disease of the Queen Square Brain Bank.

Step 1: Diagnosis of parkinsonian syndrome
- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions)

And at least one of the following:
- Muscular rigidity
- 4–6 Hz rest tremor

Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 3: Supportive prospective positive criteria of Parkinson's disease

Three or more of the following required for diagnosis of definite Parkinson's disease:
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side onset most
- Excellent response (70–100%) to L-dopa
- Severe L-dopa-induced chorea
- L-dopa response for 5 years or more
- Clinical course of 10 years or more
- Hyposmia
- Visual hallucination

Step 2: Exclusion criteria for Parkinson's disease
- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language and praxis
- Babinski signs
- Presence of a cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of L-dopa (if malabsorption excluded)
- MPTP exposure

Source: Lees AJ, Hardy J and Revesz T. Parkinson's disease. *Lancet Neurol* 2009;**373**:2055–66.

dysfunction and cognitive/psychiatric disorders such as depression, anxiety, visual hallucinations and/or dementia. Fluctuations and motor dyskinesia are very frequent and remain a challenge for the treatment.

Management of Parkinson's disease in the elderly

Pharmacological treatment

L-Dopa is the main and often only treatment for PD in the elderly. L-Dopa is a precursor of dopamine that crosses the blood–brain barrier and is used in combination with a peripheral decarboxylase inhibitor to lessen its systemic effects. The drugs used are Madopar (L-dopa + benserazide) and Sinemet (carbidopa + L-dopa). L-Dopa is effective in tremor, bradykinesia and rigidity of PD.

L-Dopa exists in several forms, distinguished by their absorption rates. Standard L-dopa is usually given the drug within 3–4 times daily, preferably 30 min before meals. In the first years of PD, most patients are controlled with 300–600 mg per day. L-Dopa should be started at low doses which can be increased very gradually until the appropriate effect is obtained. The dispersible form (dispersible Madopar) achieves peak plasma concentrations faster and can be used in early morning akinesia, in order to achieve an effect more quickly. It allows the first dose of standard L-dopa to be taken at the same time. As the disease progresses, the dose of L-dopa should be progressively increased and adverse effects are frequent. The main side effects of L-dopa are nausea and vomiting, hypotension and psychiatric disorders (hallucinations, delusions, delirium). Sedation, nightmares, vivid dreams and hallucinations could also occur as dose-related side effects. After several years of use, motor fluctuations can occur with the on–off phenomenon. Fluctuations include a delayed effect of L-dopa and wearing off between the doses. In addition, involuntary movements such as chorea, athetosis and dystonia could occur. These complications lead to revision of the timing of L-dopa administration.

Several antiparkinsonian drugs are not used in the elderly. Direct *dopamine agonists* act directly on dopamine D2 receptors. They include apomorphine, piribedil, ropinirole, lisuride and pergolide mesylate. They can be used in young persons with PD in order to delay the introduction of L-dopa, but they are not used in older persons with PD. Adverse effects are numerous and could be severe. *Anticholinergic drugs* proposed in PD to improve tremor (e.g. trihexyphenidyl and tropatepine) are never used in older persons with PD. *Selegiline* and *rasagiline* are type B monoamine oxidase inhibitors which have been proposed for neuroprotective effects in early PD.

Catechol-O-methyl transferase inhibitors (COMT-I) (entacapone and tolcapone) decrease the degradation of dopamine in the brain and increase and prolong the effect of L-dopa. They are useful in older patients with motor fluctuations and/or L-dopa-induced dyskinesia. A single tablet combining L-dopa, carbidopa and entacapone has been marketed (Stalevo) with three doses of L-dopa/carbidopa (50/12.5, 100/25, 150/37.5 mg) and fixed-dose entacapone

Table 63.4 Methods for treating non-motor symptoms and complications in Parkinson's disease; each of them should be considered after adjusting L-dopa therapy.

Condition	Treatment
Nausea, vomiting	Domperidone
Depression, generalized anxiety disorder	Selective serotonin reuptake inhibitor, psychotherapy
Hallucinations, delusions	Clozapine, quetiapine
Dementia	Rivastigmine
Orthostatic hypotension	Midodrine, droxidopa, elastic venous compression
Insomnia	Sleep hygiene, clonazepam
Constipation	Fibre intake, hydration, osmotic laxatives (macrogol)
Drooling	If severe, botulinum toxin injections in salivary glands
Urinary urgency	Anticholinergic drugs with low penetration in brain

(200 mg per tablet). This association is so far indicated in patients with PD with motor fluctuations with end dose not stabilized by L-dopa–dopa decarboxylase inhibitor. Amantadine (200–400 mg per day) was shown to be effective in lessening peak-dose dyskinesia. The dose should be adjusted in patients with renal impairment and adverse effects such as delirium are frequent in old patients.

Some other drugs might also be useful in controlling non-motor symptoms or complications (Table 63.4).

Non-pharmacological treatments

Functional neurosurgery

Bilateral deep brain stimulation of the subthalamic nucleus or globus pallidus interna produces sustained improvement in motor function, especially for symptoms that respond to L-dopa therapy, and reduces drug-induced involuntary movements. This treatment is proposed to patients who are cognitively intact and with a severe disability related to motor complications refractory to best fit treatment. Severe comorbidities are also a limitation. Hence deep brain stimulation is not currently used in elderly people with PD. Adverse effects are related to the intracranial procedure and there are some concerns about long-term safety with risks of depression and suicide. Follow-up of stimulated patients has revealed that disability progresses with time, probably in relation to neurodegeneration.

Rehabilitation and help with loss of independence

Functional rehabilitation should be started early in the disease as it helps preserve motor function. Rehabilitation sessions should preferably be held at the time of the peak effect of L-dopa. It combines specific exercises intended to sustain the maintenance of joint flexibility, walking, lifting, posture and balance, turns and drills aimed at fighting against attitudes in flexion. Speech therapy is helpful in patients with dysarthria or drooling at a later stage, and trouble with swallowing.

Loss of independence implies that human help should be organized for activities of daily living at home. In most cases, loss of independence due to motor problems can be managed at home, but professional help, caregiver involvement, meals-on-wheels and other help may be necessary. PD is not a frequent cause of admission to geriatric institutions except when severe cognitive and behavioural complications occur. PD is a chronic disease that benefits from improved coverage by national health insurance in France and in other EU countries.

Psychological support and patient education

Psychological support and patients' and caregivers' education help increase acceptance and understanding of disease and treatment and could optimize the utilization of health resources. Association of patients and caregivers could also help.

Key points

- Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease, but the exact cause remains undetermined.
- Symptoms include motor symptoms such as tremor, motion difficulties, falls and changes in gait and posture, and non-motor symptoms such as bradyphrenia, memory problems and dementia, constipation and bladder and autonomic dysfunction.
- Symptoms increase as the disease progresses.
- Parkinson's disease is responsible for severe disability after 10–15 years of progression.
- Management includes pharmacological treatment, especially with L-dopa, non-pharmacological treatment, such as functional neurosurgery, rehabilitation and help with loss of independence.

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CHAPTER 64

Non-parkinsonian movement disorders

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Introduction

Non-parkinsonian movement disorders that tend to affect primarily the elderly include chorea, restless legs and periodic leg movements during sleep and while awake, dystonia and tremor (Table 64.1).

Chorea

Chorea, derived from the Greek word for 'dance', is a continuous, random sequence of irregular, unpredictable movements that flit from one body part to another. A variety of choreatic disorders begin during childhood or early adulthood. Those that are important in the elderly include Huntington's disease (HD), senile chorea and tardive dyskinesia.

Huntington's disease

HD is an autosomal dominant neurodegenerative disorder characterized by abnormal involuntary movements, progressive dementia and psychiatric manifestations. In 1993, the specific mutation in HD was identified as an expansion of the unstable CAG trinucleotide repeat in the IT15 gene in chromosome 4p (Kremer *et al*., 1994; Hersch *et al*., 1994). Individuals with HD have more than 40 CAG repeats. There is an association of age of onset and number of repeats only in the very early and very late-onset HD (Andrew *et al*., 1993). Juvenile onset cases are associated with repeat lengths greater than 52 and paternal transmission. This preponderance of paternal transmission has been reported for cases with onset before age 21 and is due to CAG repeat length expansion during spermatogenesis (Hersch *et al*., 1994). Early onset is associated with the rigid type or Westphal variant of HD. In contrast, late-onset HD, defined as onset at age 50 or later, is associated with less than 42 repeats. Although it is believed that individuals with repeat lengths of 40 and 41 may not exhibit symptoms in their lifetime, it is unclear whether this is due to decreased penetrance among carriers with such lower repeat sizes or the mere fact that they did not live long enough. Approximately 1–2% of at-risk individuals screened for HD will have repeat lengths between 36 and 39. It is difficult to predict which of these individuals will develop symptoms of HD within a normal lifespan (Myers *et al*., 1998).

HD has a subtle, insidious onset in the third and fourth decades of life and gradually worsens over a course of 10–20 years until death. Clinically, the disease usually presents with an involuntary movement disorder characterized by chorea, dystonia, bradykinesia, incoordination and impaired postural reflexes. Oculomotor dysfunction is a frequent early sign and is characterized by slowed, delayed or inaccurate saccades. As HD advances, swallowing and speech may become impaired, eventually disrupting communication and leading to aspiration pneumonias. Intellectual decline or dementia is a uniform feature, although the severity of cognitive impairment varies among patients. Psychiatric features are also common and disabling, appearing as the presenting manifestation in up to one-third of HD patients (Biglan and Shoulson, 2002).

Approximately 25% of persons affected by the disease exhibit initial signs of chorea at age 50 or later, and half of these will not come to medical attention until after age 60. The clinical features of late-onset HD resemble those of midlife onset but the illness is more slowly progressive and less functionally debilitating. In late-onset disease, symptoms may appear to plateau or progress very slowly over several years. The most common symptoms in a series of 25 late-onset cases were mild to moderate chorea and cognitive impairment (100% of cases), dysarthria (88%) and gait disturbance (72%) (Myers *et al*., 1985). The chorea in late-onset HD often allows the patient to stay at home,

This chapter is as in the previous edition, with a list of more recent important references provided and annotated by Professor Alan Sinclair.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 64.1 Definition of movement disorders.

Disorder	Definition
Tremor	Rhythmic oscillation typically about a joint, alternating or simultaneous co-contraction of agonist and antagonist muscle groups
Chorea	Irregular, non-stereotypical quick jerks, randomly distributed
Dystonia	Sustained abnormal postures, often with a twisting character, sometimes overlying repetitive jerks

with minimal nursing support, to remain ambulatory and to maintain activities of daily living for many years.

Pathology and pharmacology

Histological studies of HD have demonstrated diffuse brain atrophy with severe neuronal loss and gliosis occurring selectively in the caudate nucleus and putamen. This neuronal loss in the striatum is largely confined to the GABAergic medium-sized spiny neurons that project to the globus pallidus, and which receive glutamergic input from the cortex and dopaminergic input from the substantia nigra. The severity of neuropathological changes was found to be closely related to the age at onset of the illness. An earlier clinical onset is associated with more severe neuropathological involvement, while older onset cases show a slower rate of progression of neuropathological changes (Myers *et al*., 1988).

The exact mechanisms that lead to the selective neuronal loss in HD are poorly understood. Hypotheses include glutamergic excitotoxicity, mitochondrial bioenergetic dysfunction, apoptosis and transcriptional dysregulation (Biglan and Shoulson, 2002). Huntingtin, the mutant protein product of CAG expansion, undergoes abnormal cleavage in the cytoplasm, resulting in the translocation of the N-terminal fragment in the nucleus and the formation of aggregates in the nucleus. It has been hypothesized that this altered cleavage and subsequent nuclear translocation represent key steps in the pathogenic cascade leading to neuronal dysfunction and cell death (Saudou *et al*., 1998).

Treatment

Currently, there is no effective treatment to slow or reverse the inexorable progression of HD. Neuroprotective strategies have been explored, including coenzyme Q10, remacemide, minocycline, creatine and Huntington's disease advocacy centre (HDAC), but none of these agents has been proven to alter the natural history of the disease, under the specific experimental conditions studied (Biglan and Shoulson, 2002). There are, however, several approaches to control the symptoms. Unfortunately, HD research has had a tendency to concentrate on the motor aspects of the disorder, whereas the major problems are behavioural (e.g. dementia, depression, psychosis) and the chorea is often the least relevant in terms of management. Chorea improves with the use of dopamine receptor-blocking agents (e.g. neuroleptics) or dopamine-depleting agents (e.g. reserpine or tetrabenazine). The newer, atypical neuroleptics, especially olanzapine, have become the drugs of choice, when treatment of chorea is needed (Bonelli *et al*., 2002; Jimenez-Jimenez *et al*., 2002; Paleacu *et al*., 2002). More recently, amantadine, an *N*-methyl-D-aspartate (NMDA) antagonist, has been found to be effective in treating chorea in patients with HD (Verhagen Metman *et al*., 2002). Management of the associated psychiatric disorders with the appropriate administration of psychotropic drugs should also be considered. Depression is managed with selective serotonin reuptake inhibitors (SSRIs) and mirtazapine, and psychosis and behavioural issues are addressed with atypical antipsychotics (Bonelli *et al*., 2004). Dementia is unfortunately the most disabling facet of this disorder and is untreatable. In fact, the most effective approach to HD available today is genetic counselling.

Spontaneous oral dyskinesia and senile chorea

Clinical features

Gowers, at the end of the nineteenth century, described an isolated form of chorea of late life as an entity separate from HD and neuroleptic use (Critchley, 1931). Isolated spontaneous oral dyskinesia (SOD) in the elderly is a clearly defined and fairly common syndrome but is more often recognized as part of other neurological syndromes such as tardive dyskinesia, Huntington's chorea, acquired hepatocerebral degeneration and complication of prolonged levodopa therapy in Parkinson's disease (PD). In some patients, the occurrence of SOD is associated with the edentulous state and the improvement with appropriate dental appliances suggests that the absence of teeth in some individuals causes or makes the clinical syndrome worse (Sutcher *et al*., 1971). In one study, observation was carried out on 1018 non-institutionalized, frail elderly subjects attending day care centres to document the prevalence of SODs. A total of 38 subjects were suspected to have SODs for a prevalence rate of 3.7% and 31 had probable tardive dyskinesia, for a prevalence rate of 3.0%. In a survey covering medical and dental issues in the same population, subjects with suspected SOD reported more frequent ill-fitting dental devices, oral pain and a lower rate of perception of good oral health compared with non-dyskinetics. Individuals with suspected SOD typically presented with mild stereotyped masticatory or labial movements compared with the more complex phenomenology of probable TD (tardive dyskinesia) cases (Blanchet *et al*., 2004).

Pathology and pathophysiology

Recent developments in molecular genetics have provided a reliable test for confirmation of the diagnosis of HD that is highly sensitive and specific. Shinotoh *et al*. (1994) measured CAG trinucleotide repeat expansion in the Huntington's gene in four cases of senile chorea, and found that CAG repetition lengths were normal. They considered this evidence that senile chorea exists as a distinct clinical entity that is nosologically separate from HD.

There is a paucity of pathological reports of senile chorea in the literature. Neuropathological cases of senile chorea reported in the past were before the advent of genetic testing for HD and it is possible that many of them represented mild cases of HD and no cognitive changes.

Treatment

Chorea can be ameliorated with neuroleptic agents. Neuroleptic agents should be initiated at low doses and slowly titrated upward to optimal symptom control. Neuroleptic use in this age group is associated with a higher incidence of TD and drug-induced parkinsonism (see Chapter 63, Parkinson's disease). Thus, the use of newer atypical neuroleptics is preferable. Although the atypical neuroleptics have been advocated to carry a much smaller risk of drug-induced parkinsonism or TD, this has not been the case with some of them. Therefore, physicians should be vigilant for the development of these complications. Amantadine is useful in ameliorating chorea, but it is excreted unchanged in the urine and it can become toxic in elderly people with decreased renal function. Anticholinergic agents and dopamine agonists tend to worsen these movements and should be avoided. Treatment of either senile chorea or SODs is indicated only if the movements are severe enough to cause functional impairment. In edentulous patients, well-fitting dentures may improve the symptoms.

Tardive dyskinesia

TD is defined as abnormal involuntary movements associated with chronic treatment with dopamine receptor-blocking agents. Neuroleptics are the most frequently implicated drugs, although other agents, for example, metoclopramide, have also been associated with the development of TD (Khot *et al*., 1992). The diagnosis of TD requires (1) history of at least 3 months total cumulative (continuous or discontinuous) neuroleptic exposure; (2) the presence of at least 'moderate' abnormal involuntary movements in one or more body areas or at least 'mild' movements in two or more body areas; (3) absence of other causes for the movements (Task Force on late Neurological effects of antipsychotic drugs, 1980). Since the earlier reports of TD, a variety of involuntary movements, in addition to the well known oral–buccal–lingual masticatory movements, have been described, including dystonia, akathisia, tics and myoclonus (Burke, 1992). It has been suggested that the newer, atypical neuroleptics (risperidone, olanzapine, quetiapine, ziprasodone, clozapine) are less likely to cause TD (Jeste, 2004; Dolder and Jeste, 2003). Clozapine and quetiapine are the ones associated with the lowest risk (Tarsy *et al*., 2002).

The typical movements of TD are choreic in speed and amplitude, but usually tend to be more stereotypic and repetitive and less random or unpredictable than chorea of other a etiologies. The orofacial and lingual muscles tend to be involved earlier and more frequently in TD. The disorder is usually only slowly progressive after initial development, and in many patients, especially the elderly, it does not appear to progress at all and may actually gradually improve with age.

Possible risk factors for TD include advanced age, female gender, affective disorder, mental retardation, brain damage, length of neuroleptic exposure, use of anticholinergic drugs, history of acute extrapyramidal side effects, antidepressant drugs, depot neuroleptics, history of drug interruptions or holidays, elevated serum neuroleptic concentrations and late-onset psychosis (Lohr and Bracha, 1988).

Studies evaluating the prevalence and risk factors for TD have been largely confounded by vague diagnostic criteria, biased study samples, lack of matched control populations and concurrent neuroleptic use, which can mask TD. Overall, most studies suggest that the average prevalence of TD is estimated as 15–20% (Khot *et al*., 1992). In one series, 45% of patients had relatively persistent symptoms over the course of 5 years, while 24% had a fluctuating course. Only 11% improved, while 7% got worse. Remissions usually appear within 1–2 years after discontinuation of medication, although they may not occur until 5 years after discontinuation of medication (Bergen *et al*., 1989).

Pathology and pathophysiology

No characteristic pathological abnormalities have been found in TD. The pathophysiology is not clearly understood. The development of dopamine receptor supersensitivity following chronic dopamine receptor blockade is hypothesized to be the mechanism underlying TD. This would explain why, as the neuroleptic agents are withdrawn and receptor blockade reduced, TD may appear for the first time, or pre-existing TD may worsen. Furthermore, exacerbation of the movements by dopaminergic agonists and improvement with increased dopamine receptor blockade or dopamine depletion support the notion that alterations in dopamine receptors are likely to be involved. As a result of the deficiencies in the dopamine supersensitivity hypothesis, attention has also been focused on other neurotransmitters, such as GABA, norepinephrine, acetylcholine and serotonin (Khot *et al*., 1992).

Treatment

Once it occurs, TD is frequently difficult to treat. Therefore, only individuals with defined indications for the use of these agents should be treated, especially among the elderly, who appear to be at a higher risk for developing TD. Although it is not proven, the neuroleptic dose should be maintained at the lowest possible and the drug should be used for the shortest period of time allowed by the patient's psychiatric disease. If the patient's psychiatric disorder is sufficiently severe to require long-term neuroleptic use, an atypical neuroleptic should be considered.

Several medications have been used in the treatment of persistent TD with variable response. These include dopamine depleters (reserpine or tetrabenazine), noradrenergic antagonists (propranolol, clonidine), γ-aminobutyric acid (GABA) agonists (clonazepam, diazepam, valproate, baclofen), botulinum toxin injections and, to a lesser degree, vitamin E, buspirone and calcium channel blockers, which have been used with variable results (Miyasaki and Lang, 1995). When the predominant movement is chorea, anticholinergic agents may worsen the movements; if, on the other hand, dystonia is the primary characteristic, these agents can be beneficial.

Restless Legs Syndrome and Periodic Limb Movements During Sleep and While Awake

Restless legs syndrome (RLS) is a sensorimotor disorder characterized primarily by motor restlessness, which is brought on by rest and accentuated later in the day and during the early night in those with normal circadian rhythms. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching. The prevalence of RLS is estimated to be 10–15% in the general population. Symptoms often begin before age 20, but usually become severe enough to seek medical attention in the fourth decade (Walters *et al*., 1996). Periodic limb movement disorder (PLMD) is frequently associated with RLS but may occur independently, especially in the elderly. The prevalence of PLMD increases with advancing age. RLS and PLMD, taken together, are the primary diagnosis in 13.3% of patients complaining of insomnia (see Chapter 54, Sleep apnoea and sleep disorders) and in 6.9% of patients complaining of excessive daytime sleepiness (Montplaisir and Godbout, 1989).

RLS and PLMD have been related to several other medical conditions, including peripheral neuropathy, iron deficiency anaemia and end-stage renal disease (Garcia-Borreguero *et al*., 2004). Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and monoamine oxidase inhibitors can induce or aggravate PLMD, as does withdrawal from anticonvulsants, benzodiazepines and barbiturates. Exacerbations of RLS can occur during pregnancy or with iron deficiency anaemia. Finally, PLMD may accompany other sleep disorders, in particular, sleep apnoea or narcolepsy (Montplaisir and Godbout, 1989).

RLS can be diagnosed by the following four clinical criteria: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching; (4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (Hening *et al*., 2004). Supportive clinical features include a positive family history, positive response to dopaminergic therapy and the presence of periodic limb movements (during wakefulness or sleep) (Hening *et al*., 2004). Family history of RLS can be found in 40–90% of patients with RLS (Montplaisir *et al*., 1997; Winkelmann *et al*., 2000). PLMD occurs in 80% of patients with RLS. The severity of RLS can vary greatly throughout a patient's lifetime but the disease is typically chronic and the course progressive. The sudden remissions, lasting for months or even years, are as difficult to explain as are the relapses, which appear without any apparent reason.

Periodic limb movements of sleep (PLMS), originally called *nocturnal myoclonus*, are best described as rhythmic extensions of the big toe and dorsiflexions of the ankle, sometimes with flexions of the knee and hip, each movement lasting 0.5–5.0 s and occurring every 20–40 s. Standard criteria for PLMS include their occurrence in a series of four or more movements spaced by intervals of 5–90 s (onset to onset) with electromyogram (EMG) burst durations of 0.5–5 s that rise to 1/4 of the EMG biocalibration amplitude (Hening *et al*., 2004). Intense movements may cause numerous arousals, leading to non-restorative sleep. PLMS may be asymptomatic, diagnosed through a bed partner's report or polysomnogram. PLMS occur primarily in stage 2, non-REM (rapid eye movement) sleep, less often in stages 3 and 4, and infrequently during REM sleep.

Fifty percent of patients with RLS have abnormal involuntary movements while awake, called *periodic leg movements during wake* (PLMW), formerly called *dyskinesias while awake*. Like the PLMS, PLMW are discrete, repetitive, stereotyped movements that recur at intervals of seconds, tend to involve primarily the legs and occur almost exclusively at rest and disappear with action. PLMW are longer compared with the leg movements during sleep (shorter than 10 s during wakefulness vs 5 s during sleep).

Differential diagnosis of RLS and PLMS should include hypnic myoclonus, fragmentary myoclonus, painful legs and moving toes syndrome, nocturnal cramps, body

jerks induced by long-term administration of levodopa or akathisia. The symptoms of akathisia are prominent throughout the waking hours of the day or night, whereas the symptoms of RLS are more prominent at night. Akathisia patients manifest the external signs of an inner urge to move, whereas patients with RLS move about to relieve the dysesthetic sensations they have in their legs.

Although our understanding of the pathophysiology and genetics of RLS has advanced considerably, there is currently no recognized objective test for the disorder. Standard sleep measures remain useful in terms of sleep initiation, continuity and sufficiency. These are often combined with measures of PLMS. Recently, the suggested immobilization test (SIT) has been proposed as a possible auxiliary measure, examining the ability of a period of imposed rest to induce subjective and motoric features of RLS. A combination of the SIT conducted in the evening with measurement of sensory discomfort and the presence of frequent PLM during awake epochs of the standard polysomnography (PSG) can provide a high degree of diagnostic accuracy (sensitivity of 82% and specificity of 100%) (Hening *et al*., 2004).

Pathophysiology and pharmacology

Several lines of evidence suggest that RLS results from dysfunction of the central rather than the peripheral nervous system. RLS improves with centrally acting dopamine agonists, and this effect can be antagonized only by centrally acting and not peripherally acting dopamine antagonists (Garcia-Borreguero *et al*., 2004). Nevertheless, the spinal cord may also be involved in the generation of PLM as they have been observed in patients with spinal cord lesions. However, treatment with dopamine agonists produces only mild improvement in the symptoms of these patients, compared with the marked response in patients with RLS (de Mello *et al*., 1996).

Neurophysiological studies, including reflex studies and studies on cortical activity, have failed to elucidate the a etiology of this syndrome. There is evidence though, obtained from functional magnetic resonance imaging (MRI), pointing towards a subcortical site as a location for the dysfunction (Bucher *et al*., 1997). It is possible that the disease arises as a result of subcortical dysfunction with state-dependent reduced spinal and cortical inhibition. In addition, the periodic nature of the PLMS reflects the disinhibition of intrinsic spinal periodic generators (Garcia-Borreguero *et al*., 2004). Functional imaging with positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have only found a modest decrease for the dopamine D2 receptor. Iron deficiency may be associated with RLS, particularly for patients with onset at a later age and family history. Decreased midbrain iron despite normal serum iron has also been demonstrated in RLS. RLS severity correlates with serum ferritin levels and oral administration of iron seems to improve RLS symptoms, especially if pretreatment ferritin levels are lower than 45 $\mu g\,l^{-1}$ (O'Keeffe *et al*., 1993; Sun *et al*., 1998). Several steps in dopaminergic pathways require normal iron levels; therefore, iron deficiency would be expected to result in dopaminergic dysfunction.

Treatment

At present, dopamine receptor agonists are the treatment of choice for RLS, particularly if daily treatment is needed or the condition is severe. This is mainly due to their longer elimination half-life, which results in less long-term complications. Several dopamine agonists have been studied under controlled conditions, showing efficacy for the treatment of the symptoms of RLS. Interestingly, cabergoline, the dopamine agonist with the longest half-life, is the only one to which no cases of augmentation have been linked so far (Garcia-Borreguero *et al*., 2004).

L-Dopa at a daily dose of 50–250 mg, in conjunction with a decarboxylase inhibitor, given as a single dose before bedtime, has been proven to be effective in producing subjective improvement of symptoms and sleep quality, shortening of sleep latency and a reduction in PLMS (Collado-Seidel *et al*., 1999). Yet, in the course of long-term treatment with L-dopa, rebound and augmentation appear. Rebound refers to the reappearance of symptoms at a time coinciding with the end of the half-life period of the drug, usually early in the morning. Augmentation reflects the occurrence of RLS symptoms earlier in the day, an overall increase in symptom severity as a result of long-term dopaminergic treatment. Augmentation frequently represents a serious problem in treating patients with RLS.

Opioids have been found to be effective in treating RLS/PLMS in a subgroup of patients and they are considered second-choice options. The required doses found to be effective are relatively high, often at the higher end of the analgesic range. Although opioids can be useful in a subpopulation of patients, the risk for abuse and the addictive potential of these compounds limit their clinical use.

Anticonvulsants such as gabapentin have been found to exert therapeutic effects. Gabapentin is particularly effective for cases associated with pain or dysaesthesia (Happe *et al*., 2001). Benzodiazepines, such as clonazepam, can be useful in ameliorating some of the symptoms of RLS, but their effects might be mediated by sleep induction rather than direct suppression of RLS symptoms.

In addition to symptomatic medication, it is important to ascertain that the body iron stores are adequate. Oral administration of iron is recommended if serum ferritin levels are lower than 45–50 $\mu g\,l^{-1}$ (O'Keeffe *et al*., 1993).

Dystonia

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures (Fahn, 1990). Dystonia is classified in three ways: by body distribution of the abnormal movements, by a etiology, and by age at onset (Table 64.2). Focal dystonia refers to the involvement of a single body area, segmental to the involvement of contiguous body areas, multifocal to the involvement of noncontiguous body areas, hemidystonia to the involvement of one arm and one leg on the same side and generalized to the involvement of one leg and trunk or two legs and an additional body area (Table 64.3). The a etiological classification divides the causes of dystonia into two major categories: idiopathic (or primary) and symptomatic (or secondary). The idiopathic group is further subdivided into familial and non-familial (sporadic) patterns.

Table 64.2 Classification of dystonia.

By age at onset
Childhood onset, 0–12 years
Adolescent onset, 13–20 years
Adult onset, >20 years
By cause
Idiopathic
Sporadic
Familial
Symptomatic
By distribution
Focal
Segmental
Multifocal
Generalized
Hemidystonia

Table 64.3 Classification of dystonia according to distribution.

Focal dystonia: single body part
Blepharospasm: eyelids
Oromandibular dystonia: mouth
Spasmodic dysphonia: larynx
Torticollis: neck
Writer's cramp: arm
Segmental dystonia: two or more contiguous body parts
Meige syndrome: eyes and mouth
Generalized dystonia: one leg and trunk or both legs and another body part
Childhood-onset hereditary torsion dystonia
Multifocal dystonia: two or more noncontiguous body parts
Hemidystonia: ipsilateral arm and leg

Dystonia beginning in childhood usually starts in the legs and progresses to become generalized or multifocal. Early-onset primary torsion dystonia usually starts around age nine and has a genetic background in the great majority of cases. Approximately 80–90% of Ashkenazi Jewish children and 50% of non-Jewish children test positive for the DYT1 defect. The remaining cases are either non-genetic or belong to less common (e.g. DYT6, DYT13) or still unknown genetic causes of dystonia (Ozelius *et al*., 1997). In contrast, adult-onset dystonia is usually sporadic. The onset of dystonic symptoms is usually gradual, with slow progression over the first 5–10 years. Although the dystonia may slowly worsen or spread to an adjacent body area, it seldom generalizes in the adult. Up to 33% of dystonic patients may experience a partial or complete remission, but this is rarely permanent (Greene *et al*., 1995).

The most frequent primary focal dystonia seen in a movement disorder clinic is spasmodic torticollis or cervical dystonia (CD). CD is a focal dystonia affecting the muscles of the neck and upper torso. Depending on the specific pattern of muscles involved, it can produce turning of the head (torticollis), tilting of the head towards the shoulder (laterocollis) and flexion (antecollis) or extension (retrocollis) of the head (Bressman and Greene, 2000).

The second most frequent dystonic syndrome seen in the adult is blepharospasm. Blepharospasm is manifested by increased blinking, clonic eye closure or sustained, tonic eye closure. In some patients, reading, driving or watching a movie may be impossible. The severity of the spasms can be such that can render the patient functionally blind. The association of blepharospasm with lower facial or oromandibular dystonia is referred to as Meige's or Bruegel's syndrome. Oromandibular dystonia involves the muscles of facial expression or the masticatory and other oral muscles. Clinically, patients have involuntary grimacing, puckering, frowning, jaw opening or closing, tongue protrusions and a variety of other movements that may be exacerbated by the use of the muscles. In addition to social embarrassment, it may impair speaking, eating and drinking.

Spasmodic dysphonia is a focal dystonia of the laryngeal muscles resulting in either a strained and choked or quiet and breathy voice, depending on the dystonic position of the vocal cords (adductor or abductor, respectively). Limb dystonia can affect either the upper or lower extremity, and is usually task-specific. The most common form is writer's cramp.

Pathology and pathophysiology

Pathological studies have been carried out on patients with primary torsion dystonia and there are no consistent pathological abnormalities identified by light microscopy (Gibb *et al*., 1988). Studies in symptomatic hemidystonia show lesions of the putamen, the thalamus and the connections of

the basal ganglia with the thalamus and the cortex (Marsden *et al*., 1985). Although autopsy studies have shown variable changes in norepinephrine, there have been no consistent neurochemical changes described in idiopathic dystonia. The lack of sufficient brain specimens has hindered further pathologic studies.

PET using fluorodeoxyglucose (FDG) in 11 patients with unilateral dystonia compared with 11 age-matched controls showed a relative metabolic overactivity of the lentiform nucleus and premotor cortices (Eidelberg *et al*., 1995). Pathophysiological, mechanisms have been suggested by electrophysiological studies. Electomyography shows prolonged co-contracting bursts of activity in agonist and antagonist muscles and frequent spread of activity to distal muscles not normally used in a particular movement. These abnormalities can be explained by a loss of inhibitory control at the segmental (spinal cord, brainstem) or cortical level (Berardelli *et al*., 1998).

The DYT1 gene encodes for a protein, torsin A. In normal adult brain, torsin A is widely distributed, with intense expression in the substantia nigra compacta, cerebellar dentate nucleus, Purkinje cells, basis pontis, locus ceruleus, numerous thalamic nuclei, the pedunculopontine nucleus, the oculomotor nuclei, the hippocampal formation and the frontal cortex. Although the exact function of torsin A remains elusive, speculation on the mechanism the mutant torsin A compromises cellular function includes disrupted processing of normal torsin A or other proteins, interference with membrane trafficking and formation of cytoplasmic inclusions (Walker *et al*., 2002).

Treatment

Treatment of dystonia has had limited success. Pharmacological treatment of dystonia is largely based on empirical, rather than scientific rationale. Anticholinergic medications, such as trihexyphenidyl, have been found to be of benefit in 67% of patients with idiopathic dystonia studied, mean age 18.6 years (Greene *et al*., 1988). In the elderly, the side effects from anticholinergics are frequent and often dose-limiting. These include sedation, mental clouding, dry eyes and mouth, blurred vision, urinary retention and constipation. Other agents reported anecdotally to be of benefit include baclofen, tizanidine, clonazepam, tetrabenazine, reserpine, tegretol, lithium and bromocriptine. Although dopamine receptor-blocking agents have been used, the risk of TD has traditionally precluded routine administration of these agents. The newer, atypical neuroleptics, which carry less of a risk for tardive syndromes, can be an alternative approach. Patients with dopa-responsive dystonia manifested as childhood-onset dystonia with diurnal fluctuations and associated parkinsonism may respond dramatically to low doses of levodopa (Nutt and Nygaard, 2001).

The introduction of botulinum toxin into clinical practice in the late 1980s revolutionized treatment of focal dystonia. Botulinum toxin, when injected locally, blocks acetylcholine release at the neuromuscular junction and, therefore, weakens the muscle. It has been successfully used in the treatment of most forms of focal or segmental dystonia (Comella and Pullman, 2004; Goldman and Comella, 2003), although it does not provide any permanent benefit or change in prognosis.

When drugs are ineffective or have shortcomings, surgical approaches can be considered. The procedure of choice currently is deep brain stimulation (DBS) of the internal segment of the globus pallidum (GPi). Bilateral pallidal lesions can be associated with significant adverse effects including speech difficulties and cognitive disturbances. It is for this reason that neurosurgeons have sought to develop surgical procedures that offer the efficacy of selective pallidal lesions but have a better index of safety. With the introduction of DBS to treat first chronic pain and then PD, it became logical to apply DBS to treat dystonia. There is now increasing experience in the use of DBS to treat various forms of dystonia. The initial results suggest that certain primary dystonias can show a strong improvement with GPi DBS (Lozano and Abosch, 2004).

Tremor

Tremor is a rhythmic, oscillatory movement produced by alternating or synchronous contractions of antagonistic muscles. Tremor is considered the most common movement disorder. Tremors can be classified according to their phenomenology, distribution, frequency or a etiology. Phenomenologically, tremors are categorized as rest, postural, and kinetic tremors (Lang *et al*., 1992) (Table 64.4). Rest tremor is defined as tremor occurring when the affected body part is in complete repose. The classic example of a rest tremor is found in PD. Postural tremor is defined as tremor occurring during maintenance of an antigravity posture. Essential tremor (ET) is the prototype. ET is primarily a postural tremor, although it may be present to a lesser degree during movement, particularly when the

Table 64.4 Tremor classification.

Tremor type	Description	Associated disorder
Rest tremor	Large amplitude; 4–6 Hz	Parkinsonism rubral tremor
Postural tremor	Amplitude varies; 6–12 Hz	Essential tremor
Kinetic tremor	Large amplitude; 3–4 Hz	Cerebellar tremor

movement involves postural adjustments. ET is familial in approximately half of the patients, with an autosomal dominant inheritance pattern. Some studies have suggested that there is an association between ET and dystonia, and between ET and parkinsonism. On the basis of an analysis of 678 patients diagnosed as ET, 6.1% were found to have concomitant PD and 6.9% had coexisting dystonia (Koller *et al*., 1994).

ET is more common in the upper extremities, although legs, head, trunk, face and vocal cords may be affected. Although sometimes referred to as benign, the symptoms result in major disability in up to 15% of those afflicted, with 3% of patients being completely disabled. Over time, it tends to progress slowly with long periods of stable symptoms intervening. Alcohol suppresses the tremor for a few hours in 30–60% of patients (Boecker *et al*., 1996).

Kinetic tremor is seen with voluntary movement, during the initiation (initial tremor) the course of the movement (dynamic tremor) and as the affected part approaches a target. Clinical–anatomical correlations indicate that kinetic tremor is usually associated with lesions of the cerebellum or the cerebellar outflow pathways. Lesions of the cerebellar hemispheres or upper brainstem may cause kinetic tremors with a frequency ranging from 5 to 7 Hz. Caudal brainstem lesions may cause faster tremors, ranging from 8 to 12 Hz (Cole *et al*., 1988).

Task- or position-specific tremors occur either during a specific task, for example, writer's tremor, or while maintaining a position, for example, orthostatic tremor. In 1984, Heilman described a tremor occurring after a few seconds of standing, which would progressively increase unless the patient began to walk, at which time the tremor ceased and the gait was normal (Heilman, 1984). Usually, patients with orthostatic tremor have normal clinical examination except for wide base standing and unsteadiness, which disappear when walking. Arm tremor resembling ET is found present in one-third of cases. Electrophysiological exploration is necessary for diagnosis and shows a regular rapid tremor (frequency around 16 Hz) in the weight-bearing muscles (Sander *et al*., 1998; Mastain *et al*., 1998). Orthostatic tremor cannot be considered as a clinical variant of postural essential tremor. Its pathophysiology is unknown, but the efficacy of clonazepam, primidone barbiturates suggests the impairment of the gabaergic system.

Tremor is widely experienced in neurologically intact individuals undergoing intense anxiety or stress, with the use of drugs (Table 64.5), and with other metabolic derangements. Non-pathological tremor has a low amplitude and a high frequency (Marsden, 1984).

Table 64.5 Non-parkinsonian movement disorders associated with selected drugs.

Disorder	Drug
Tremor	Amphetamines
	Bronchodilators
	Sympathomimetics
	Lithium
	Tricyclic antidepressants
	Selective serotonin reuptake inhibitors
	Valproic acid
	Corticosteroids
Chorea	Levodopa
	Dopamine agonists
	Anticholinergics
	Neuroleptics (tardive)
	Metoclopramide (tardive)
	Estrogens
	Amphetamines
	Anticonvulsants
Dystonia	Neuroleptics (acute and tardive)
	Metoclopramide (aute and tardive)
	Levodopa
	Dopamine agonists
	Chloroquine
Tics	Neuroleptics (tardive)
	Metoclopramide (tardive)
	Cocaine
	Amphetamines
	Lamotrigine

Pathophysiology and pharmacology

The mechanism underlying ET is not known. It has been hypothesized that the tremor arises from abnormal spontaneous firing of the inferior olivary nucleus, which drives the cerebellum and its outflow pathways via thalamus to the cerebral cortex and then to the spinal cord. The involvement of the olivo–cerebellar–thalamo–cortical circuitry in ET is supported by changes in the cerebellar blood flow as measured by PET. Using a higher-resolution camera, the investigators were additionally able to demonstrate bilateral midbrain activation in the region of the red nuclei during tremor, without change in the activity of the inferior olive (Wills *et al*., 1995).

The neurochemical abnormality underlying ET may relate to the adrenergic system. This is based on clinical observations of improvement in tremor using β-adrenergic antagonists and tremor induction when using β-adrenergic antagonists (Koller *et al*., 2000a).

Treatment

Treatment of ET is indicated if the symptoms are sufficiently severe to interfere with daily activities or threaten job security. Propanolol is considered the treatment of choice. It is started at a low dose and is gradually increased until clinical benefit, side effects, or a maximal dose of 320 mg

is reached. β-Blockers are contraindicated in patients with broncho-constrictive disorders, peripheral vascular disease and congestive heart failure, and relatively contraindicated in diabetes mellitus. If propanolol is ineffective or contraindicated, primidone may provide symptomatic relief. The starting dose is 25–50 mg once daily with a slowly increasing dose schedule until clinical benefit or side effects occur. The major drawback of primidone is the occurrence of sedation, although small increments in the dose may avoid this side effect. Other drug alternatives include clonazepam, methazolamide, flunarizine, nimodipine and gabapentin. All these have been tried in small numbers of patients with variable results.

Surgical treatment for ET has been used since the early 1950s. The optimal target has been determined to be the ventralis intermedius (VIM) nucleus of the thalamus. Thalamotomy improves contralateral tremor in more than 90% of patients. Long-term studies of thalamotomy indicate that the benefits continue in most patients. Persistent morbidity associated with thalamotomy, which occurs in less than 10% of patients, includes dysarthria, dysequilibrium, weakness and cognitive impairment. Bilateral thalamotomy is associated with substantial morbidity and is usually avoided. Chronic stimulation of the VIM is a safe and effective alternative to thalamotomy. Adverse effects of chronic stimulation include paresthesia, dysarthria, dysequilibrium and localized pain. DBS of the VIM nucleus of the thalamus appears to be safer than thalamotomy and is now the recommended procedure of choice (Koller *et al*., 2000b; Koller *et al*., 2001; Pahwa *et al*., 2000).

Key points

- Chorea in the elderly is a clearly defined and fairly common syndrome but is more often recognized as part of other neurological syndromes such as tardive dyskinesia, Huntington's chorea, acquired hepatocerebral degeneration and complication of prolonged levodopa therapy in PD.
- The clinical features of late-onset HD resemble those of midlife onset, but the illness is more slowly progressive and less functionally debilitating.
- TD is frequently difficult to treat, therefore only individuals with defined indications for the use of these agents should be treated, especially among the elderly, who appear to be at a higher risk for developing TD, and atypical neuroleptics should be the agents of choice.
- RLS is a sensorimotor disorder characterized primarily by motor restlessness, which is brought on by rest and relieved by movement, such as walking or stretching. PLMD is frequently associated with RLS but may occur independently, especially in the elderly. Both RLS and PLMD are treated with dopaminergic agents.
- Dystonia in the elderly appears mostly as focal or segmental dystonia and not generalized. It can be treated with botulinum toxin injections or medications.
- Tremor is a frequent occurrence in the elderly and can be seen as rest tremor, in PD, postural and kinetic tremor, in ET and as a side effect of medications, intention tremor in situations associated with cerebellar lesions, and task or position-specific tremor, in dystonia.

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Walters AS, Hickey K, Maltzman J *et al*. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. *Neurology* 1996;**46**:92–5.

Wills AJ, Jenkins IH, Thompson PD *et al*. A positron emission tomography study of cerebral activation associated with essential and writing tremor. *Archives of Neurology* 1995;**52**:299–305.

Winkelmann J, Wetter TC, Collado-Seidel V *et al*. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. *Sleep* 2000;**23**:597–602.

Annotated recent references

A striatal asymmetry index is being investigated as a tool for differentiating PD from non-PD tremor syndromes. This involves examining nigro-striatal uptake of [^{123}I]-FP-CIT-SPECT.

Sixel-Döring F, Liepe K, Mollenhauer B *et al*. The role of (123)I-FP-CIT-SPECT in the differential diagnosis of Parkinson and tremor syndromes: a critical assessment of 125 cases. *J Neurol* 2011;**258**:2147–54.

Transcranial brain parenchyma sonography (TCS) is another recent tool being evaluated to differentiate between idiopathic Parkinson's disease (PD) and essential tremor (ET).

Doepp F, Plotkin M, Siegel L *et al*. Brain parenchyma sonography and ^{123}I-FP-CIT SPECT in Parkinson's disease and essential tremor. *Mov Disord* 2008;**23**:405–10.

Routine brain MRI has limited added value for differentiating between PD and AP when clinical certainty is already high, but has some diagnostic value when the clinical diagnosis is still uncertain.

Meijer FJ, Aerts MB, Abdo WF *et al*. Contribution of routine brain MRI to the differential diagnosis of parkinsonism: a 3-year prospective follow-up study. *J Neurol* 2011 Oct 19. Epub ahead of print.

Tetrabenazine continues to be investigated for its established antichorea efficacy in Huntington's disease. The drug has also been reported to also be effective in a variety of other hyperkinetic movement disorders, including tardive dyskinesia and tics associated with Tourette's syndrome.

Jankovic J and Clarence-Smith K. Tetrabenazine for the treatment of chorea and other hyperkinetic movement disorders. *Expert Rev Neurother* 2011;**11**:1509–23.

It has been demonstrated that gait bradykinesia and dynamic balance impairments begin in the presymptomatic stage of HD and continue to worsen in the symptomatic stages. Various gait measures are sensitive in differentiating between mutation positive and negative individuals even if impairments are not detected by clinical neurological examination.

Rao AK, Muratori L, Louis ED *et al*. Spectrum of gait impairments in presymptomatic and symptomatic Huntington's disease. *Mov Disord* 2008;**23**:1100–7.

In the Nurses Health Study II, greater frequency of restless legs symptoms was associated with higher concurrent systolic and diastolic blood pressures (p trend: <0.0001 for both). Women with restless legs syndrome appear to have a higher prevalence of hypertension, and this prevalence increases with more frequent restless legs symptoms.

Batool-Anwar S, Malhotra A, Forman J *et al*. Restless legs syndrome and hypertension in middle-aged women. *Hypertension* 2011;**58**:791–6.

It has been demonstrated that deep brain stimulation (DBS) plus unilateral ventralis oralis thalamotomy for cerebral palsy patients with fixed states in the upper extremities is useful not only to treat secondary dystonic movement but also to improve quality of life. In some patients with secondary (post-traumatic) dystonia and tardive dyskinesia, excellent clinical outcomes have been achieved using a stereotactic procedure.

Kim JP, Chang WS and Chang JW. Treatment of secondary dystonia with a combined stereotactic procedure: long-term surgical outcomes. *Acta Neurochir (Wien)* 2011;**153**:2319–27; discussion 2328. Epub 2011 Sep 11.

CHAPTER 65

Diabetic neuropathy

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Introduction

Diabetic neuropathies (DNs) encompass a wide range of nerve abnormalities and prevalence rates reported are between 5 and 100%, depending on diagnostic criteria used.[1–3] DNs affect both peripheral and autonomic nervous systems and cause considerable morbidity and mortality in both type I and type II diabetic patients. DNs account for more hospitalizations than all other diabetic complications combined and are responsible for 50–75% of non-traumatic amputations.[4,5] In older adults who have diabetes, peripheral neuropathies (PNs) are especially troublesome because of their detrimental effects on stability, sensorimotor function, gait and activities of daily living (ADLs).[6–8] The incidence of distal symmetric neuropathy rises dramatically with increasing age after 65 years in both diabetic and non-diabetic men and women, with a higher incidence among older adults with diabetes (32.2, 95% CI 21.7–42.7 versus 5.8, 95% CI 4.3–7.8, per 1000 person-years).[9] Diabetes accounted for 39% of prevalent and 49% of incident cases of neuropathy in older adults,[9] emphasizing diabetes as a critical although not sole risk factor. In the USA for 1999–2000, 28% of adults aged 70–79 years and 35% of adults aged >80 years had PN, based on a simple screen for reduced sensation at the foot.[10] In this chapter, we present and discuss the most recent approaches to the treatment of the common forms of diabetic neuropathy, including symmetric, focal and diffuse neuropathies (Box 65.1, Figure 65.1). We also provide the reader with algorithms for the recognition and management of common pain and entrapment syndromes and a global approach to the recognition of syndromes requiring specialized treatments based upon our improved understanding of their aetiopathogenesis. A comprehensive evaluation of autonomic neuropathy is beyond the scope of this chapter, but the reader is referred to two excellent reviews on this topic.[11,12].

Pathogenic mechanisms

Figure 65.2 shows our current view on the pathogenesis of DPN. The aetiology includes metabolic; vascular; autoimmune; oxidative and nitrosative stress; and neurohormonal growth factor deficiency. Inflammation is more clearly involved in the specific inflammatory neuropathies such as vasculitic and granulomatous disease than in DPN *per se*,[13] although this has not been studied in age-related neuropathies. P- and E-selectin and VCAM-1 activated during the inflammatory process predict the decline in peripheral nerve function among diabetic patients.[14] Impaired blood flow and endoneurial microvasculopathy, mainly thickening of the blood vessel wall or occlusion, play a critical role. Metabolic disturbances in the presence of an underlying genetic predisposition cause reduced nerve perfusion. Both animal and human studies have shown major defects arising from chronic hyperglycaemia and altered lipid metabolism.[15] Oxidative/nitrosative stress-related mechanisms are also important in vascular dysfunction and tend to increase vasoconstriction. Improving nerve blood flow may improve nerve conduction velocity in DPN.[16] Oxidative and nitrosative stress and inflammation are implicated in several neurodegenerative disorders, including Alzheimer's disease and amyotrophic lateral sclerosis (ALS),[17] and in DPN.[18,19] Potentially, similar mechanisms play a role in the peripheral nerve with ageing. As ageing[20] and type 2 diabetes[21–25] are associated with increased levels of subclinical systemic inflammatory markers, such as

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Box 65.1 Classification of diabetic neuropathy[a].

Focal neuropathies
- Mononeuritis
- Entrapment syndromes

Diffuse neuropathies
- Proximal motor (amyotrophy)
  - Coexisting chronic inflammatory demyelinating polyneuropathy (CIPD)
  - Monoclonal gammopathy of undetermined significance (MGUS)
  - Circulating GM1 antibodies and antibodies to neuronal cells
  - Inflammatory vasculitis

Generalized symmetric polyneuropathies
- Acute sensory
- Autonomic
- Chronic sensorimotor distal polyneuropathy (DPN)
  - Large fibre
  - Small fibre

Adapted from Thomas[117] and Vinik.[37]

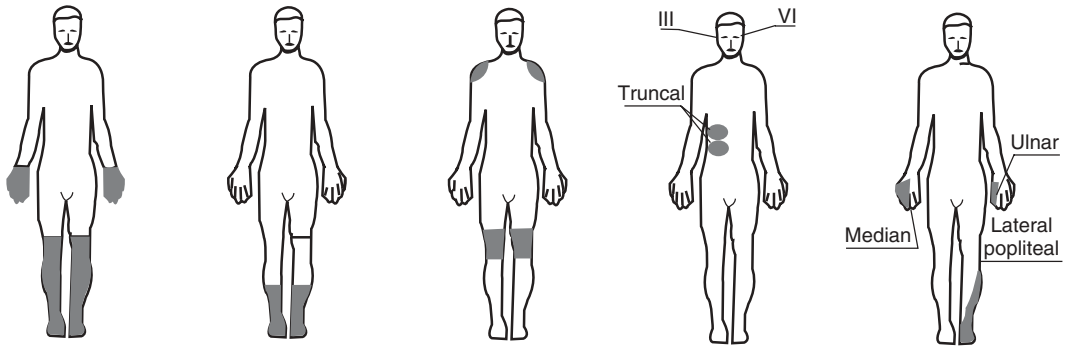
cytokines IL-6 and TNF-α, and acute-phase proteins such as CRP. An Italian population-based study found that high levels of sIL-6R and lower vitamin E were significantly related to lower nerve conduction velocity.[26]

Clinical presentation and diagnosis

Focal neuropathies (mononeuropathies and entrapment syndromes)

Mononeuropathies occur primarily in older adults. Their onset is generally acute and associated with pain and they heal spontaneously, usually within 6–8 weeks. These neuropathies are caused by vascular obstruction, typically in the cranial nerves III, VI and VII, ulnar, median and peroneal. Mononeuropathies must be distinguished from entrapment syndromes, which start slowly, progress and persist without intervention (Table 65.1).

Common entrapment sites in diabetic patients involve the median, ulnar and peroneal nerves, the lateral cutaneous nerve of the thigh and the tibial nerve in the tarsal canal. Their onset is gradual and is usually limited to a single nerve.[27] Carpal tunnel syndrome is the most common entrapment syndrome, affecting one in three diabetic patients.[28] It occurs three times more frequently in patients with diabetes compared with the normal healthy population[29] and may be related to diabetic cheiroarthropathy, repeated undetected trauma, metabolic changes or an accumulation of fluid or oedema within the confined space of the carpal tunnel.[30] Surgical treatment of entrapment syndrome neuropathies is effective, but the decision to proceed with surgery should be based on severity of symptoms, appearance of motor weakness and failure of non-surgical treatment, and there must be electrophysiological evidence of nerve entrapment.



Large fibre neuropathy	Small fibre neuropathy	Proximal motor neuropathy	Acute mono neuropthies	Pressure palsies
Sensory loss: 0 → +++ (touch, vibration) Pain: + → +++ Tendon reflex: N → ↓↓↓ Motor deficit 0 → +++	Sensory loss: 0 → + (thermal, allodynia) Pain: + → +++ Tendon reflex: N → ↓ Motor deficit: 0	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: ↓↓ Proximal motor deficit: + → +++	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: N Motor deficit + → +++	Sensory loss in nerve distribution: + → +++ Pain: + → ++ Tendon reflex: N Motor deficit + → +++

Figure 65.1 Schematic representation of different clinical presentations of diabetic neuropathy. Reprinted from Vinik *et al.*, *Medical Clinics of North America* 2004;**88**:947–99. Copyright 2004, with permission from Elsevier.

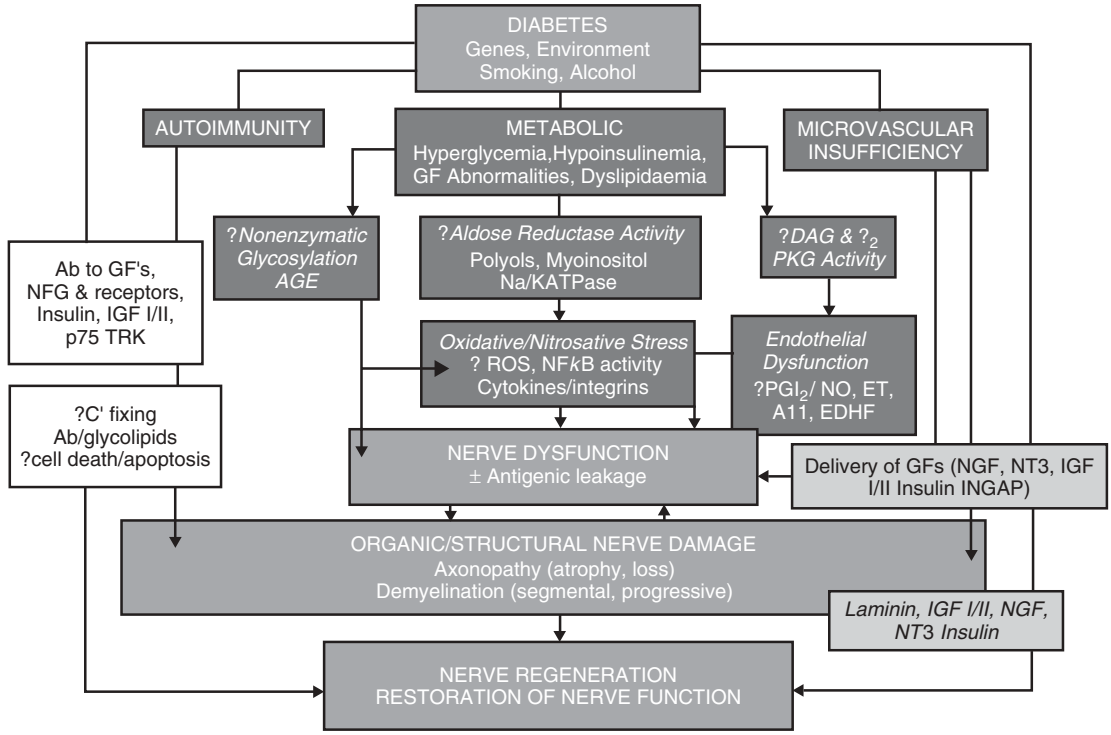


Figure 65.2 Pathogenesis of diabetic neuropathies based upon autoimmunity, metabolic and microvascular insufficiency.[121] Ab, antibody; AGE, advance glycation end products; C′, complement; DAG, diacylglycerol; ET, endothelin; EDHF, endothelium-derived hyperpolarizing factor; GF, growth factor; IGF; insulin-like growth factor; NFkB, nuclear factor κB; NGF, nerve growth factor; NO, nitric oxide; NT3, neurotropin 3; PKC, protein kinase C; PGI2, prostaglandin I2; ROS, reactive oxygen species; TRK, tyrosine kinase.

Table 65.1 Comparison of features of mononeuropathies, entrapment syndromes and distal symmetrical polyneuropathy.

Feature	Mononeuropathy	Entrapment syndrome	Neuropathy
Onset	Sudden	Gradual	Gradual
Pattern	Single nerve but may be multiple	Single nerve exposed to trauma	Distal symmetrical polyneuropathy
Nerves involved	CN III, VI, VII, ulnar, median, perineal	Median, ulnar, peroneal, medial and lateral plantar	Mixed, motor, sensory, autonomic
Natural history	Resolves spontaneously	Progressive	Progressive
Treatment	Symptomatic	Rest, splints, local steroids, diuretics, surgery	Tight glycaemic control, pregabalin, duloxetine, antioxidants, 'nutrinerve', research drugs
Distribution of Sensory loss	Area supplied by the nerve	Area supplied beyond the site of entrapment	Distal and symmetrical. 'glove and stocking' distribution

Reproduced from Vinik A *et al.*,[121] Chapter 35, with permission.

Diffuse neuropathies (proximal motor neuropathies)

Proximal motor neuropathy can be clinically identified based on proximal muscle weakness and muscle wasting. It may be symmetric or asymmetric in distribution and is sometimes associated with pain in the lateral aspect of the thigh. Patients usually present with weakness of the iliopsoas, obturator and adductor muscles, together with relative preservation of the gluteus maximus and minimus and hamstrings.[31,32] Those affected have great difficulty rising out of a chair unaided, although heel or toe standing is surprisingly good. In the classic form of diabetic proximal motor neuropathy, axonal loss is the predominant process and the condition coexists with distal symmetric

polyneuropathy.[33] Electrophysiological evaluation reveals lumbosacral plexopathy.[34] Common features include the following:

- Primarily affects the elderly.
- Onset may be gradual or acute.
- Begins with pain in the thighs and hips or buttocks.
- Pain followed by significant weakness of the proximal muscles of the lower limbs with inability to rise from a sitting position (positive Gower's manoeuvre).
- Begins unilaterally and spreads bilaterally.
- Coexists with DPN.
- Spontaneous muscle fasciculation or provoked by percussion.

Proximal motor neuropathy is now recognized as being secondary to a variety of causes unrelated to diabetes, but which occur more frequently in patients who have diabetes than in the general population. It includes patients who have CIDP, MGUS, circulating GM1 antibodies and antibodies to neuronal cells and inflammatory vasculitis.[35,36] Vinik[37] found that almost half of patients with proximal neuropathies have a vasculitis and all but 9% have CIDP, MGUS or a ganglioside antibody syndrome.[37,38] Sharma *et al*.[39] examined over 1000 patients who had neurological disorders and found that CIDP was 11 times more frequent among diabetic than non-diabetic patients.

In contrast, if demyelination predominates and the motor deficit affects proximal and distal muscle groups, the diagnosis of CIDP should be considered. It is important to divide proximal syndromes into these two subcategories because the CIDP variant responds dramatically to intervention,[37,39,40] with IVIG, plasmapheresis, steroids and immunosuppressive agents,[37] whereas proximal motor neuropathy runs its own course over months to years. Until more evidence is available, we consider them as separate syndromes.

These conditions should be distinguished from spinal stenosis syndromes common in older individuals, which occur because of (1) encroachment on nerve roots as they emerge from the spinal cord, (2) osteophytes that narrow joint space and cause compression, (3) hypertrophy of the ligamentum flavum by ageing, (4) disk dehydration due to ageing and (5) arachnoiditis. If compression occurs at the level of T12 and L1/2, the vascular system may be involved. This often causes claudication during downhill walking and is relieved with spinal flexion. Nerve root compression is more typical at L5/S1 and therefore in difficult cases it may be necessary to obtain an MRI of the lumbosacral spine. Diagnosis is critical because therapy may range from simple physical therapy to surgical decompression if symptoms are severe or if motor paralysis exists.

Chronic sensorimotor distal polyneuropathy

Chronic sensorimotor DPN is the most common and widely recognized form of diabetic neuropathy. The onset is usually insidious, following stress or initiation of therapy for diabetes. DPN may be either sensory or motor and may involve small fibres, large fibres or both.[41] Initial neurological evaluation should focus on detection of the specific part of the nervous system affected by diabetes. Most patients with DPN have a combination of both large and small nerve fibre involvement (Figure 65.3).

Large fibre neuropathies

A majority of neuropathies in older adults involve large fibres. Large fibre neuropathies may involve sensory and/or motor nerves and most patients will present with a 'glove and stocking' distribution of sensory loss.[42] These tend to be the neuropathies of signs rather than symptoms.

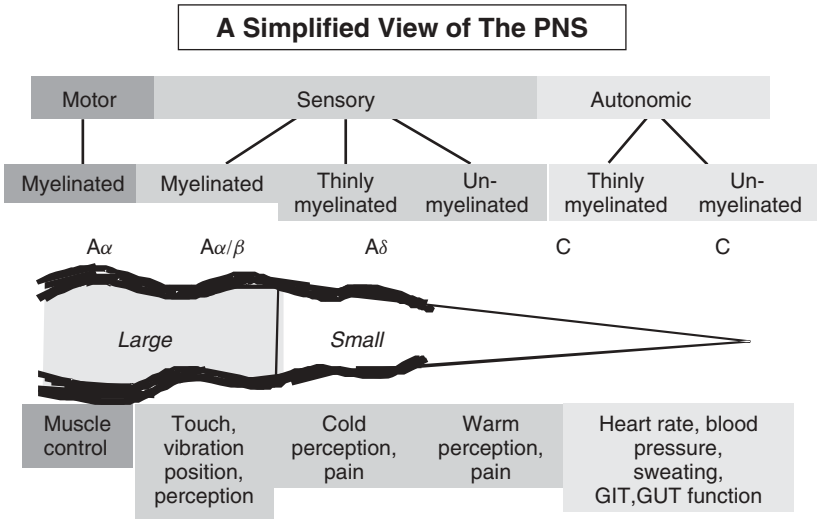


Figure 65.3 Schematic presentation of the physiological function of different nerve fibres.[121] Aα fibres are large myelinated fibres, in charge of motor functions and muscle control. Aα/β fibres are also large myelinated fibres, with sensory functions such as perception to touch, vibration and position. Aδ fibres are small myelinated fibres, in charge of pain stimuli and cold perception. C fibres can be myelinated or unmyelinated and have both sensory (warm perception and pain) and autonomic functions (blood pressure and heart rate regulation, sweating, etc.). GIT, gastrointestinal tract; GUT, genitourinary tract.

Table 65.2 Decline in neurological function between 20 and 80 years of age.

Function	Dysfunction (%)
Vibratory sensation	97
Stability (rombergism)	32
Handwriting speed	30
Handgrip strength	22
Ankle jerk	9
Ataxia (finger–nose test)	8
Pain perception	0

Data from references 118–120.

They are manifested by reduced vibration (often the first objective evidence of neuropathy) and position sense, weakness, muscle wasting and depressed tendon reflexes. Early in the course of the neuropathic process, multifocal sensory loss might also be found (Table 65.2) The symptoms may be minimal, such as a sensation of walking on cotton, floors feeling 'strange', inability to turn the pages of a book or inability to discriminate among coins. In some patients, severe distal muscle weakness can accompany the sensory loss, resulting in an inability to stand on the toes or heels.

Little is known, however, at the clinical and population levels about the role of age-related loss in peripheral nerve function to sarcopenia and loss of strength associated with ageing. Loss of lean mass, or sarcopenia, is thought to account for much of the loss of strength and function in older adults.[43,44] In addition to lower mass, ageing muscle is characterized by loss of muscle fibres, predominantly type 2 fast-twitch fibres and an increase in grouping or 'clustering' of type 1 fibres.[45] These changes are thought to be caused in part by disuse atrophy and in part to drop out of the anterior horn motor neurons at the level of the spinal cord. When the motor neuron is lost with disease (polio, ALS) or ageing, remaining motor neurons can sprout new dendritic connections to 'orphaned' muscle fibres. This reinnervation process may be responsible for the increase in grouping of type 1 fibres and may limit regaining type 2 fibres after loss caused by atrophy. Although the innervation of muscle tissue is essential to its function, very little is known about the relative contribution of peripheral nerve function to muscle function and functional decline in community-dwelling older adults. In diabetes, severe PN is clearly related to muscle atrophy.[46] Recent work in epidemiological cohort studies of older adults indicates that poorer motor nerve function is related to lower calf muscle density[47] and poorer sensory and motor nerve function is related to lower quadriceps and ankle strength, independent of diabetes and peripheral arterial disease status.[48] Given the known atrophy and denervation in the pathophysiological description of muscle ageing, it is remarkable how little is known at the clinical and population levels about the role of age-related loss in nerve function to the age-related loss of muscle mass and strength. This neurogenic process may be a critical link in the pathogenesis of sarcopenia and mobility loss in old age.

Older adults who have large fibre neuropathies have difficulty stabilizing their bodies when walking on irregular surfaces, with concomitant impairment of reaction time and balance.[6] This lack of peripheral sensory input increases the risk of falling and fracture in these patients. In the Women's Health and Ageing study, women with diabetes reported difficulty in performing 14 of 15 daily tasks, which included walking two to three blocks, lifting 10 pounds, using a telephone and bathing.[7] Failure to perform basic ADLs readily compromises an individual's independence and quality of life (QOL), which increases mortality and morbidity in this susceptible population.[49] The Norfolk QOL tool is used to measure patients' perception of the effects of diabetes and diabetic neuropathy.[49]

Epidemiological studies have found that older adults with poor peripheral nerve function have worse physical performance, balance, muscle density and bone density.[22,23,47,50,51] Most of these associations were independent of diabetes status. A twofold higher prospective decline in motor performance exists for older adults who have distal symmetrical neuropathy.[52] Older women with PN have significantly greater step width:length ratio and step-time variability, less efficient gait and lower gait speed compared with controls.[8,53] Clinical consequences of higher fall and fracture rates are also evident in older adults who have peripheral nerve impairments.[54–58]

In recent years, several inexpensive devices have been developed for the assessment of somatosensory function, including vibration, thermal energy and light-touch perception. These instruments allow for the non-invasive assessment of cutaneous sensory functions, which correlate with specific neural fibre function. In addition to the above modalities, quantitative sensory tests (QSTs) are available for the assessment of pain threshold and cutaneous current perception.[41] Clinical manifestations of large fibre neuropathies include the following:

- impaired vibration perception and position sense;
- depressed tendon reflexes;
- dull (like a toothache), crushing or cramp-like pain in the bones of the feet;
- sensory ataxia (waddling like a duck);
- wasting of small muscles of feet with hammertoes and weakness of hands and feet;
- shortening of the Achilles tendon with equinus;
- increased blood flow to the foot (hot foot) with increased risk of Charcot neuroarthropathy.

Small fibre neuropathies

Small nerve fibre dysfunction usually occurs early and is often present without objective signs or electrophysiological evidence of nerve damage.[41] It manifests first in the lower limbs with symptoms of pain and hyperalgesia, followed by a loss of thermal sensitivity and reduced light-touch and pinprick sensation.[59] Small unmyelinated C-fibres control pain sensation, warm thermal perception and autonomic function. A patient who has early damage to these nerves may experience burning, dysesthetic pain, often accompanied by hyperalgesia, and allodynia. This pain is distinct from that of large fibre neuropathy, in which the pain is usually described as deep and 'gnawing'. Because peripheral sympathetic nerve fibres are also comprised of small, unmyelinated C-fibres, it is not surprising that pain is improved with sympathetic blocking agents (e.g. beta-blockers, calcium channel blockers).

It should be noted that dry, cracked skin and impaired skin blood flow in the feet, together with impaired sympathetic regulation of sweat glands and anteriovenous (AV) shunt vessels in the feet, create a favourable environment for bacteria. In the absence of pain, which occurs with the depletion of substance P, patients may be led to believe that their neuropathy has subsided, when in fact it is progressing. These patients may also display decreased thermal pain thresholds, which may be caused in part by the decrease in nerve growth factor (NGF) that maintains small fibre neurons. The clinical manifestations of small fibre neuropathies can be summarized as follows:

- prominent pain: burning and superficial and associated with allodynia; i.e. interpretation of all stimuli as painful (e.g. touch);
- hypoalgesia late in the condition;
- defective autonomic function with decreased sweating, dry skin, impaired vasomotion and blood flow and cold feet;
- intact reflexes, motor strength;
- silent electrophysiology;
- absence of objective signs reduced sensitivity to 1.0 g Semmes–Weinstein monofilament and pricking sensation using the Waardenberg wheel or similar instrument;
- as the condition progresses, abnormal thresholds for warm thermal perception, neurovascular function, pain, quantitative sudorimetry and quantitative autonomic function tests;
- increased risk of foot ulceration and subsequent gangrene.

Differential diagnosis

Diabetes as the cause of neuropathy is diagnosed by exclusion of various other causes of neuropathy. In those patients who have diabetes and neuropathy who present with symptoms of distal symmetric sensorimotor deficit, differential diagnosis should include hereditary sensory neuropathies, vitamin B_{12} and folate deficiency, syphilis, Lyme disease, neuropathy associated with IgM monoclonal gammopathy of undetermined significance (IgM MGUS neuropathy), other paraneoplastic conditions, autoimmune diseases and toxic neuropathies. In patients who have one or more motor neurological syndromes, chronic motor neuropathies, acute inflammatory demyelinating polyneuropathy (AIDP), CIDP and immunoglobulin G (IgG) and IgA MGUS neuropathies should actively be sought (Table 65.3).

Recent evidence supports an autoimmune aetiology for neuropathy in AIDS, Lyme disease, AIDP, CIDP, multifocal motor neuropathy, MGUS neuropathies and even diabetic polyneuropathy.[30,42] Hence an intensive workup for humoral immune mechanisms should be performed. If any of these conditions are found, the appropriate therapeutic regime for the specific disease must be instituted before embarking on a regime of diabetic neuropathy management. It is not always possible to determine the exact cause of neuropathy if monoclonal gammopathy and diabetes coexist in the same patient. A course of intravenous

Table 65.3 Differential diagnosis of distal symmetric polyneuropathy.

Type	Syndrome
Congenital/familial	Charcot–Marie–Tooth
Traumatic	Entrapment syndromes
Inflammatory	Sarcoidosis
	Leprosy
	Lyme disease
	HIV
Neoplastic	Carcinoma – paraneoplastic syndromes
	Myeloma, amyloid
	Reticuloses, leukaemias, lymphomas
Metabolic/endocrine	Diabetes mellitus
	Uraemia
	Pernicious anaemia (vitamin B_{12} deficiency)
	Hypothyroidism
	Porphyria (acute intermittent)
Vascular	Diabetes, vasculitis
Toxic	Alcohol
	Heavy metals (lead, mercury, arsenic)
	Hydrocarbons, chemotherapeutic drugs
Autoimmune	Diabetes
	PLA syndrome
	Chronic inflammatory demyelinating neuropathy
	Multifocal motor neuropathy
	Guillain–Barré syndrome

(i.v.) immunoglobulin or immunosuppression should be attempted, depending on the class of monoclonal antibody.

Nerve tissue biopsy may be helpful for excluding other causes of neuropathy and in the determination of predominant pathological changes in patients who have complex clinical findings as a means of dictating choice of treatment.[40,60] The authors' laboratory performs nerve biopsies only when non-invasive neurological procedures fail to provide an answer or when extensive evaluation is necessary for scientific purposes.[60] We expect a further increase in our dependence on histopathological and ultrastructural examination of nerve tissue for differentiation of neuropathic syndromes as our knowledge of pathophysiological and clinical complexity among diabetic neuropathic variants increases. Figure 65.4 depicts a diagnostic algorithm for the assessment of neurological deficit and classification of neuropathic syndromes.

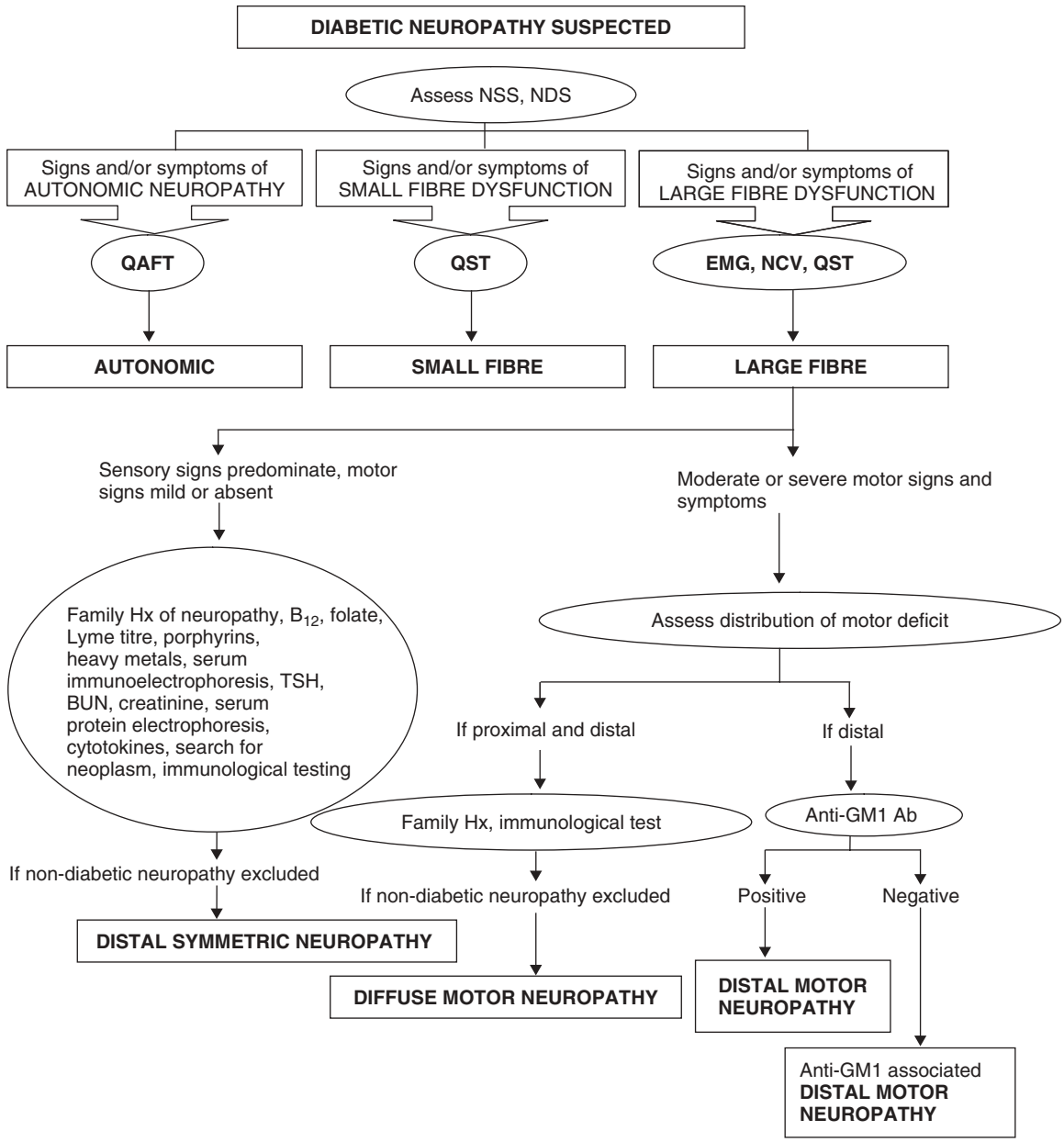


Figure 65.4 Diagnostic algorithm for assessment of neurological deficit and classification of neuropathic syndrome.[1] NSS, neurological symptom score; NDS, nerve disability score; QST, quantitative sensory test; QAFT, quantitative autonomic function test; EMG, electromyography; NCV, nerve conduction velocity.

Charcot neuroarthropathy

Charcot neuroarthropathy is a progressive condition associated with prolonged neuropathy and characterized by pathological fracture, joint dislocation and, if left untreated, disabling joint deformity. The most common location for Charcot neuroarthropathy is in the foot. The prevailing theory of Charcot progression suggests that autonomic neuropathy causes increased blood flow to the extremities, which increases bone resorption and causes osteopenia. Subsequent motor neuropathies cause muscular imbalance, which place abnormal stress on the affected extremity. Sensory neuropathies prevent the patient from sensing abnormal changes in the joints and bones, which may occur because of minor trauma, such as during walking.[61] It is further hypothesized that Achilles tendon shortening due to destruction of collagen fibres may be caused by accumulation of advanced glycation end products (AGEs).[62,63]

Patients with Charcot neuroarthropathy may present acutely with severe pain (or no pain if severe sensory neuropathy), a warm-to-hot swollen foot with increased skin blood flow (despite decreased warm[64] sensory perception and vibration detection) and possible radiographic evidence of osteopenia. The acute Charcot foot can mimic cellulitis or, less commonly, deep vein thrombosis, so these should be investigated first. It should also be noted that radiographic findings can be normal in the acute phase, with subsequent films showing severe subluxation or fracture. Strict immobilization and protection of the foot using a total contact cast are the recommended approach to treating acute Charcot neuroarthropathy. Pain and inflammation respond to bisphosphonates (e.g. slow i.v. pamidronate infusion over 12 h) within 3–4 weeks.[65] It should be noted that oral bisphosphonates may cause oesophageal dysfunction and increase the risk of obstruction and perforation. Achilles tendon shortening producing equinus is correctable by surgical lengthening and may prevent further progression. Patient education, protective footwear and routine foot care are required to prevent further complications such as foot ulceration. In cases of severe joint and bony destruction, reconstructive surgery is effective in salvaging the limb and improving mobility and QOL.[49]

Management of neuropathy

The high prevalence of certain subclinical diseases in the elderly may be associated with declines in peripheral nerve function. Importantly, these conditions are modifiable, so early intervention against these risk factors may prevent peripheral nerve function declines and the subsequent clinical consequences associated with PN. Vitamin B_{12} deficiency is a known cause of clinical neuropathy;[66] however, the impact of marginally poor vitamin B_{12} levels, found in 22–35% of community-dwelling older adults,[67–69] on peripheral nerve decline is unknown. Low vitamin B_{12} levels were associated with missing ankle tendon jerks among those aged 75 years and older.[70] There is emerging evidence that the dose and duration of metformin therapy reduces vitamin B_{12} and worsens neuropathy.[71] This has clear clinical implications for defining vitamin B_{12} replacement criteria.[72]

Nearly all peripheral arterial disease (PAD) in the elderly is subclinical, with 98% asymptomatic.[73] An Italian study in community-dwelling elderly found an association between subclinical PAD and poor nerve function.[74] This finding is of particular importance because 12% of older adults aged 70–79 years and 22% of those aged 80 years or more in the USA have subclinical PAD.[10] Subclinical PAD is underappreciated clinically, but highly preventable.[75,76]

The metabolic syndrome represents another prevalent risk factor for peripheral nerve impairments in the elderly. The prevalence of the metabolic syndrome in the USA is >40% in adults aged 60 years or older.[77] It is a risk factor for PN among diabetic adults.[78,79] In the Cardiovascular Health Study of older adults, participants who had normal glucose metabolism or a mildly elevated impaired fasting glucose (IFG) had lower heart rate variability (HRV), a marker of cardiovascular autonomic neuropathy, in the presence of two or more components of the metabolic syndrome.[80] In addition to the reduction of blood glucose levels, prevention and treatment of the other components of the metabolic syndrome (obesity, lipid abnormalities and high blood pressure) could be targeted to prevent peripheral nerve declines in older adults.

Once the diagnosis of neuropathy has been made, therapy to reduce symptoms and prevent further progression should be initiated. Diabetic patients who have large fibre neuropathies are incoordinate and ataxic and are 17 times more likely to fall than their non-neuropathic counterparts.[81] Older subjects have a higher incidence of neuropathy than younger subjects, especially involving large fibres. It is vitally important to improve strength and balance in the patient with large fibre neuropathy. Older adults who have or do not have neuropathy can benefit from high-intensity strength training by increasing muscle strength, improving coordination and balance and thus reducing fall and fracture risk.[82–84] Low-impact activities that emphasize muscular strength and coordination and challenge the vestibular system, such as pilates, yoga and Tai Chi, may also be particularly helpful. Strategies for management of large fibre neuropathies include the following:

- strength, gait and balance training;
- pain management as detailed below;
- orthotics fitted with proper shoes to treat and/or prevent foot deformities;

- tendon lengthening for equinus caused by Achilles tendon shortening;
- bisphosphonates to treat osteopenia;
- surgical reconstruction and full contact casting as necessary.

Strategies for the management of small fibre neuropathies include simple measures that can protect the foot deficient in functional C-fibres from developing ulceration and therefore, gangrene and amputation:

- Foot protection is of the utmost importance. Wearing padded socks can promote ulcer healing and/or reduce the likelihood of developing one.[85]
- Supportive shoes with orthotics if necessary.
- Regular foot and shoe inspection. Patients should inspect the plantar surface of their feet with a mirror on a daily basis (many are too obese to see their feet, let alone the undersurface).
- Extreme caution to prevent heat injury. Patients should test the bathwater with a part of the body that is not insensate before plunging a numb foot into the water. Patients should also be cautioned against falling asleep in front of the fireplace with their insensate feet close to the fire.
- Emollient creams should be used to moisturize dry skin and prevent cracking and infection.

Therapies aimed at pathogenic mechanisms

Retrospective and prospective studies have suggested a relationship between hyperglycaemia and the development and severity of diabetic neuropathy and significant effects of intensive insulin treatment on the prevention of neuropathy.[86] Intensive treatment of hyperglycaemia in the elderly is controversial. Additionally, no epidemiological or natural history study has defined the importance of late-onset diabetes in aged populations and IFG as risk factors for nerve function decline in very old adults. Recent data from the Cardiovascular Health Study suggest that IFG is a risk factor for autonomic neuropathy in the elderly.[80]

Studies in animal models and cultured cells provide a conceptual framework for the cause and treatment of diabetic neuropathy; however, the limited translational work in diabetic patients continues to generate debate over the cause of human diabetic neuropathy and to date we have no effective long-term treatment. Several clinical trials have found that treating oxidative stress may improve peripheral and autonomic neuropathy in type 2 diabetic adults.[19,87–89] Thiazolidinediones reduce hyperglycaemia through reductions in insulin resistance and may also reduce chronic inflammation, potentially impacting pathways leading to PN.[90–92] Exciting emerging evidence indicates that fibrates and statins are protective for peripheral nerve function decline in type II diabetic adults.[93,94] Older adults using statins show a greater benefit than younger adults because of their higher attributable risk of cardiovascular disease;[95] however, the impact of statins on PN in the elderly has not yet been evaluated. Unfortunately, no drugs that have been studied in clinical trials aimed at treating the pathogenic mechanisms of DPN have been approved by the US Food and Drug Administration (FDA).

The role of exercise and balance training for older adults with PN is promising. Several small studies in diabetic patients found that aerobic exercise improved quantitative test results for peripheral nerve function[96,97] and cardiac autonomic neuropathy.[98] Exercise may have an important role in the primary prevention of peripheral and cardiac autonomic nervous system decline. Among diabetic participants and/or those with PN, balance training is effective in improving balance outcomes and likely reducing risk of falls.[82,99,100]

Therapy aimed at treating symptoms in patients who have sensorimotor distal polyneuropathy

It is critical to discern the underlying condition in diabetic patients who have pain. Physicians must be able to differentiate painful diabetic neuropathy from other unrelated or coexisting conditions in patients who have diabetes. The most common of these are claudication, Morton neuroma, Charcot neuroarthropathy, fasciitis, osteoarthritis and radiculopathy (Table 65.4).

Treatment strategies should aim to decrease the afferent input, reduce local inflammation, suppress sympathetic fortification of the stimulus, reduce the impact of excitatory amino acids, alter the modulation of nociceptors and suppress Na^+ channel activity (Figure 65.5).

Amitriptyline is prescribed for diabetic neuropathy,[101] but anticholinergic side effects such as orthostatic hypotension and possible cardiac arrhythmias[101,102] warrant caution in its use. Contraindications to amitriptyline and other tricyclic antidepressants include cardiac conduction block, long QT syndrome, myocardial infarction within 6 months and ventricular arrhythmias or frequent premature ventricular contractions.[102] Older adults who have neuropathy are at risk for adverse events from tricyclic antidepressants, especially stability, balance and cognitive problems.[103] For this reason, patients over 40 years old should have a screening electrocardiogram before using these medications.[103]

Other commonly used drug classes include analgesics (local, simple and narcotic), antiarrhythmics and antiepileptic drugs (Table 65.5).[102] Based on positive results from randomized controlled trials and expert clinical opinion of members of the faculty of the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain, recommendations for first-line medications for neuropathic pain include gabapentin, 5% lidocaine patch, opioid analgesics, tramadol hydrochloride and

Table 65.4 Common pain syndromes similar to painful diabetic neuropathy.

Condition	Key characteristics and differentiating features
Claudication	Doppler ultrasonography confirms clinical diagnosis of arterial occlusion Diabetic patients may present with normal extremities and absent foot pulses Peripheral arterial occlusion with underlying atherosclerosis Usually intermittent, worsened by walking; remits with rest; other signs/symptoms suggest arterial insufficiency
Morton's neuroma	Benign neuroma formation on third plantar interdigital nerve Generally unilateral More frequent in women Pain elicited when pressure is applied with the thumb between the first and fourth metatarsal heads
Osteoarthritis	Can be secondary to diabetes mellitus, but onset of pain is usually gradual and in one or two joints Differential diagnosis based on X-ray Morning stiffness, diminished joint motion and flexion contractures Pain worsens with exercise and improves with rest Radiculopathy can result
Radiculopathy	Can be caused by diabetes, but also from arthritis or metastatic disease Neurological examinations and imaging can localize lesion site Pain can occur in thorax, extremities, shoulder or arm, depending on site of lesion
Charcot neuroarthropathy	May result from osteopenia due to increased blood flow following repeated minor trauma in individuals with diabetic neuropathy Warm to hot foot with increased skin blood flow Decreased warm sensory perception, vibration detection
Plantar fasciitis	Pain in plantar region of the foot Tenderness along plantar fascia when ankle is dorsiflexed Shooting or burning in the heel with each step Worsening pain with prolonged activity Often associated with calcaneal spur on radiography
Tarsal tunnel syndrome	Caused by entrapment of the posterior tibial nerve Pain and numbness radiate from beneath the medial malleolus to the sole Clinical examination includes percussion, palpation for possible soft-tissue matter, nerve conduction studies, magnetic resonance imaging

tricyclic antidepressants.[103] Consideration of the safety and tolerability of different therapies is important in avoiding adverse effects, a common result of treatment of neuropathic pain. Dosages must be titrated based on positive response, treatment adherence and adverse events.[103]

Anti-epileptic drugs (AEDs) have a long history of effectiveness in the treatment of neuropathic pain. Since 1993, nine new AEDs (felbamate, gabapentin, pregabalin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine and zonisamide) have received FDA approval for the adjunctive treatment of partial seizures[104] (see Table 65.5) Three of these drugs have also been approved for generalized seizures (felbamate, lamotrigine and topiramate) and three (felbamate, lamotrigine and oxcarbazepine) for monotherapy.[104] Principal mechanisms of action include sodium channel blockade (felbamate, lamotrigine, oxcarbazepine, topiramate and zonisamide), potentiation of γ-aminobutyric acid (GABA) activity (tiagabine and topiramate), calcium channel blockade (felbamate, lamotrigine, topiramate and zonisamide), antagonism of glutamate at *N*-methyl-D-aspartate (NMDA) receptors (felbamate, memantine and dextromethorphan) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (felbamate and topiramate) and mechanisms of action still undetermined (gabapentin and pregabalin, levetiracetam). Only two drugs have been approved by the FDA for the treatment of painful diabetic neuropathy, pregabalin and duloxetine. The serotonin/norepinephrine receptor inhibitor (SNRI) pregabalin produced significant improvements in pain scores within 1 week of treatment, which persisted for 6–12 weeks in four randomized controlled trials including 146–724 patients who had diabetic neuropathy.[105–108] Adverse events included dose-related somnolence, ataxia and confusion, peripheral oedema and constipation. A recent Canadian study evaluated cost-effectiveness of pregabalin versus gabapentin for the treatment of painful DN, concluding that pregabalin was more cost-effective than gabapentin.[109]

Lamotrigine (200–400 mg daily) is an anticonvulsant with dual-action inhibition of neuronal hyperexcitability. Two randomized placebo-controlled studies including 720 patients showed that the drug was inconsistently effective for the treatment of pain when compared with placebo, although it was generally safe and well tolerated.[110]

In addition to providing efficacy against epilepsy, these new AEDs may also be effective in treating neuropathic pain. For example, the AED lamotrigine may decrease hyperexcitability in dorsal horn spinal neurons by inhibiting glutamate release-2 mechanisms and decrease spontaneous activity in regenerating primary afferent nerve fibres.[111] In addition, the 'wind-up' phenomenon caused by nerve injury and the kindling that occurs in hippocampal neurons in patients with mesial temporal sclerosis both

Table 65.5 Drugs approved by the FDA for treatment of neuropathic pain syndrome.

Medication	Indication	Beginning dosages	Titration	Maximum dosage	Duration of adequate trial
Gabapentin	Post-herpetic neuralgia	100–300 mg every night or 100–300 mg 3× per day	Increase by 100–300 mg 3× per day every 1–7 days as tolerated	3600 mg per day (1200 mg 3× per day); reduce if low creatinine clearance	3–8 weeks for titration plus 1–2 weeks at maximum tolerated dosage
Pregabalin	DPN	50 mg 3× per day	Increase up to 100 mg 3× per day	600 mg per day	Start with 50 mg t.i.d. and increase up to 100 mg t.i.d. over 1 week
Lamotrigine	Post-herpetic neuralgia	200–400 mg every night	Start with 25–50 mg every other day and increase by 25 mg every week	500 mg per day	3–5 weeks for titration and 1–2 weeks at maximum tolerated dosage
Carbamazepine[a]	Trigeminal neuralgia	200 mg per day (100 mg b.i.d.)	Add up to 200 mg per day in increments of 100 mg every 12 h	1200 mg per day	
Duloxetine	DPN	30 mg	30 mg weekly	120 mg	2 weeks
5% lidocaine patch	Post-herpetic neuralgia	Maximum of three patches daily for a maximum of 12 h	None needed	Maximum of three patches daily for a maximum of 12 h	2 weeks
Opioid analgesics[b]	Moderate to severe pain	5–15 mg every 4 h as needed	After 1–2 weeks, convert total daily dosage to long-acting medication as needed	No maximum with careful titration; consider evaluation by pain specialist at dosages exceeding 120–180 mg per day	4–6 weeks
Tramadol hydrochloride	Moderate to moderately severe pain	50 mg 1 or 2× per day	Increase by 50–100 mg per day in divided doses every 3–7 days as tolerated	400 mg per day (100 mg 4× per day); in patients older than 75 years, 300 mg per day in divided doses	4 weeks
Tricyclic antidepressants (e.g. nortriptyline hydrochloride or desipramine hydrochloride)	Chronic pain	10–25 mg every night	Increase by 10–25 mg per day every 3–7 days as tolerated	75–150 mg per day; if blood level of active drug and its metabolite is $<100\ ng\ ml^{-1}$, continue titration with caution	6–8 weeks with at least 1–2 weeks at maximum tolerated dosage
Duloxetine	Diabetic neuropathic pain	30 mg b.i.d.	Increase to 60 b.i.d. No further titration		4 weeks
Serotonin/ norepinephrine Reuptake inhibitor					
Fluoxetine	Diabetic neuropathic pain	30 mg b.i.d.	Increase to 60 b.i.d. No further titration		4 weeks
Serotonin/ norepinephrine Reuptake inhibitor					

[a]Source: Tegretol (prescribing information), Novartis Pharmaceuticals, East Hanover, NJ, USA, 2003.
[b]Dosages given are for morphine sulfate.

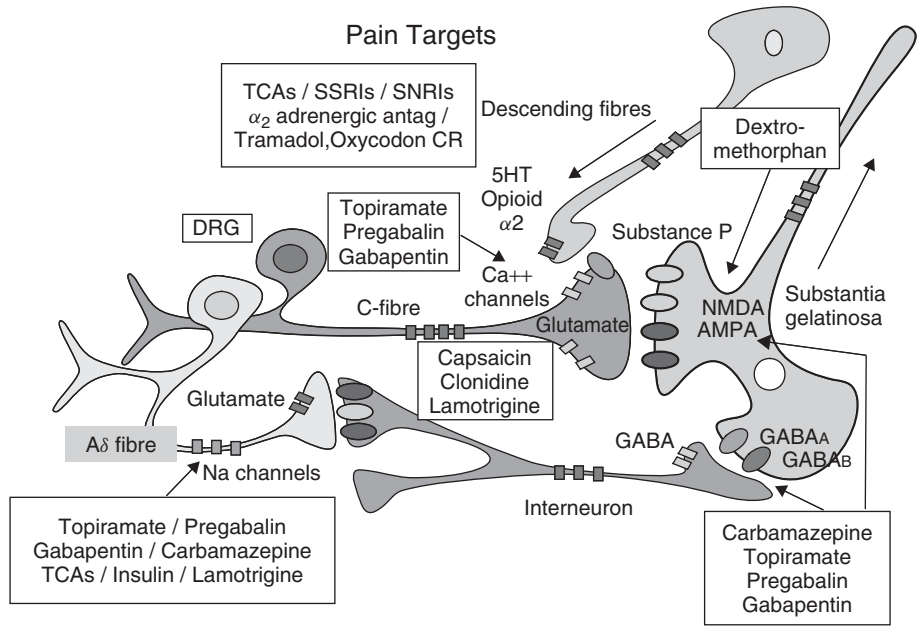


Figure 65.5 Different mechanisms of pain and possible treatments.[121] C fibres are modulated by sympathetic input with spontaneous firing of different neurotransmitters to the dorsal root ganglia, spinal cord and cerebral cortex. Sympathetic blockers (e.g. clonidine) and depletion of axonal substance P used by C fibres as their neurotransmitter (e.g. by capsaicin) may improve pain. In contrast, Ad fibres utilize Na^+ channels for their conduction and agents that inhibit Na^+ exchange such as antiepileptic drugs, tricyclic antidepressants and insulin may ameliorate this form of pain. Anticonvulsants (carbamazepine, gabapentin, pregabalin, topiramate) potentiate activity of γ-aminobutyric acid, inhibit Na^+ and Ca^{2+} channels and inhibit *N*-methyl-D-aspartate receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. Dextromethorphan blocks *N*-methyl-D-aspartate receptors in the spinal cord. Tricyclic antidepressants, selective serotonin reuptake inhibitors (e.g. fluoxetine) and serotonin and norepinephrine reuptake inhibitors inhibit serotonin and norepinephrine reuptake, enhancing their effect in endogenous pain-inhibitory systems in the brain. Tramadol is a central opioid analgesic. α_2 adrenergic antag, α_2 adrenergic antagonists; 5HT, 5-hydroxytryptamine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DRG, dorsal root ganglia; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; SNRIs, serotonin and norepinephrine reuptake inhibitors; SP, substance P; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

enlist activation of NMDA receptors[112] that can be affected by felbamate.[104]

The evidence supporting the use of AEDs for the treatment of PN continues to evolve. Patients who have failed one anticonvulsant may respond to another, because drugs in this class often have different mechanisms of action.[103] When these mechanisms are understood, it may prove beneficial to combine drugs for a synergistic effect. For example, a sodium channel blocker such as lamotrigine may be used with a glutamate antagonist such as felbamate. In addition, certain drugs may possess multiple mechanisms of action which increases its likelihood of success (e.g. topiramate). If pain is divided according to its derivation from different nerve fibre types (e.g. Aδ versus C-fibre), spinal cord or cortical, then different types of pain should respond to different therapies (Figure 65.6).

Duloxetine has recently been approved for neuropathic pain in the USA. The efficacy and safety of duloxetine were evaluated in three controlled studies using doses of 60 and 120 mg per day over 12 weeks.[113] In all three studies, the average 24 h pain intensity was significantly reduced with both doses compared with placebo treatment. The response rates defined as $\geqslant$ 50% pain reduction were 48.2% (120 mg per day), 47.2% (60 mg per day) and 27.9% (placebo), giving a number-needed-to-treat (NNT) of 4.9 (95% CI, 3.6 – 7.6) for 120 mg per day and 5.2 (95% CI, 3.8–8.3) for 60 mg per day.[114] Patients with higher pain intensity tend to respond better than those with lower pain levels.[115] Most frequent adverse effects include nausea, somnolence, dizziness, constipation, dry mouth and reduced appetite. Physicians must be alert to suicidal ideation and exacerbation of autonomic symptoms and also aggravation of depression in patients with bipolar tendencies.

Although it would be preferable to rely on FDA-approved medications for the treatment of DN, no drugs have yet received an indication for this purpose. As shown in Table 65.5, only a few drugs, including two AEDs, have received FDA approval for the treatment of chronic neuropathic pain syndromes.[104] Carbamazepine has FDA approval for the treatment of trigeminal neuralgia and is

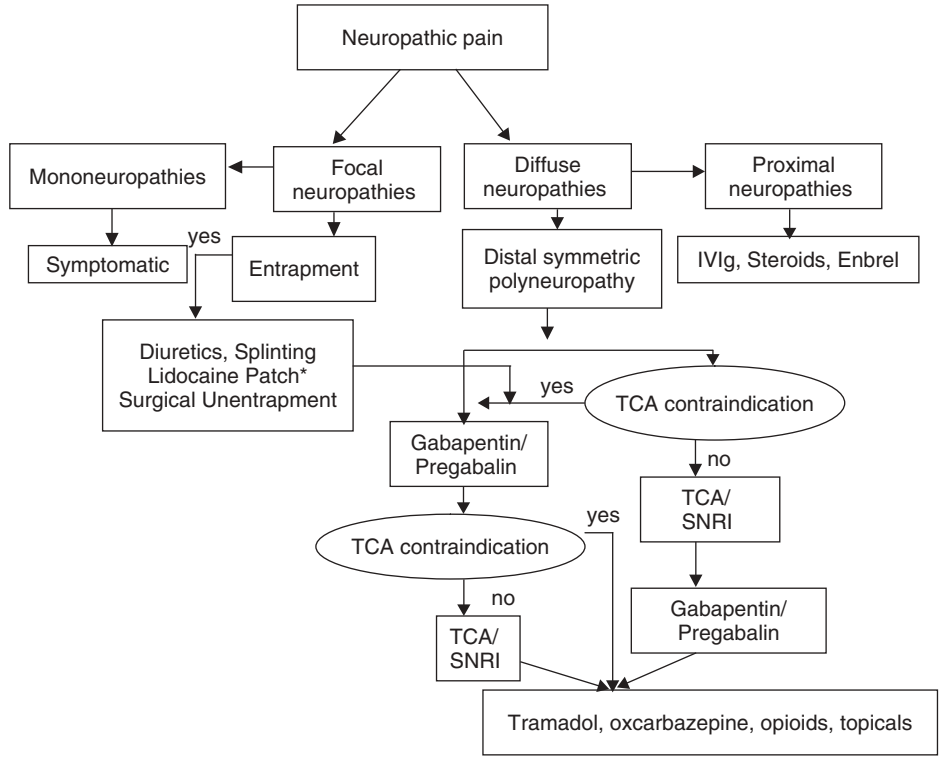


Figure 65.6 Algorithm for the management of symptomatic diabetic neuropathy. Non-pharmacological, topical or physical therapies can be useful at any time (capsaicin, acupuncture, etc.). The only two drugs approved by in the USA for the treatment of painful diabetic neuropathy are pregabalin and duloxetine. However, based on the NNT (number-needed-to-treat), tricyclic antidepressants are the most cost-effective. SNRIs, serotonin and norepinephrine reuptake inhibitors. Reproduced from A. Vinik, The approach to the management of the patient with neuropathic pain, *J Clin Endocrinol Metab* 2010;**1**:1–5. Copyright 2010, The Endocrine Society.

effective in controlling the lightning pain of DPN, and both gabapentin and 5% lidocaine patch[103] are approved for post-herpetic neuralgia.[103] The SNRI duloxetine is also approved for DPN, post-herpetic neuralgia and fibromyalgia.

Special considerations

Carbamazepine, an Na^+ channel blocker, is effective against trigeminal neuralgia, but is being replaced with the safer oxcarbazine, which is useful for 'lightning'-type pains. Lamotrigine may cause skin rashes if titrated up too rapidly and gabapentin, whose action still remains obscure and may cause serious central nervous system (CNS) side effects, failed in one of three studies and causes weight gain. Dextromethorphan, an NMDA receptor antagonist, was relatively weak and its successor memantine has not undergone successful trials. Topical capsaicin (three teaspoons of cayenne pepper + one jar of cold cream) depletes substance P, but is difficult to use and can be dangerous if it contacts mucous membranes. Results from topical lidocaine or it oral equivalent mexilitine are equivocal. The anticonvulsant drug topiramate has been used successfully to treat pain in diabetic patients and also promotes weight loss and restful sleep, suggesting that the drug may have other beneficial effects apart from relieving pain.[116] Tramadol and oxycodone are weak opioids which have also shown to be effective but require careful titration and observation.

Conclusion

Diabetic neuropathy is a heterogeneous disease with diverse pathology. Recognition of the clinical homologue of these pathological processes is the first step in achieving the appropriate form of intervention. Treatment should be individualized such that the particular manifestation and underlying pathogenesis of each patient's unique clinical presentation is considered. In older adults, special care should be taken to manage pain while optimizing daily function and mobility, with the fewest adverse side effects from medication. Older adults are at great risk for falling and fractures due to instability and weakness and require strength exercises and coordination training. Ultimately,

agents that address large fibre dysfunction will be essential if we are to reduce the gross impairment of QOL and ADLs that neuropathy visits upon the older person who has diabetes.

Key points

- Diabetic neuropathy is a common heterogeneous disorder.
- Neuropathy increases the risk of falls and fractures and requires that older persons have strength exercises and coordination training.
- Numerous drugs may ameliorate pain symptoms due to neuropathy.
- Diabetic neuropathies can effect the autonomic nervous system, small and large neurons.

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CHAPTER 66

Disorders of the neuromuscular junction

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Introduction

The most common adult-onset disorders of neuromuscular transmission are myasthenia gravis (MG)[1] and the Lambert–Eaton myasthenic syndrome (LEMS). Both conditions are antibody mediated and arguably the best understood of all neurological autoimmune diseases. The membrane ion channels and receptors at the neuromuscular junction (NMJ) seem particularly vulnerable to attack from circulating autoantibodies, perhaps because these structures lie outside the blood–nerve barrier. The most common, but not exclusive, target antigen in MG is the postsynaptic muscle nicotinic acetylcholine receptor (AChR) and in LEMS the targets are presynaptic neuronal voltage-gated calcium channels. In addition, antibodies to neuronal voltage-gated potassium channels are the most common cause of the neuromyotonia clinical variant of peripheral nerve hyperexcitability (PNH) and are also responsible for a non-paraneoplastic limbic encephalitis.

Myasthenia gravis

Clinical features

MG was possibly first described by Thomas Willis in the seventeenth century (*De Anima Brutorum*, 1672), but was only named as such by Jolly in 1895. The overall incidence of MG is between 2 and 10 per 100 000 people. It affects all races and can begin at any age after the first year of life. However, incidence is markedly age dependent, with about half of patients presenting after the age of 40 years. The condition is markedly underdiagnosed in people over the age of 75 years.[2] There are peaks of incidence at both 10–30 years and over the age of about 60 years in patients not harbouring an underlying thymoma, whereas onset of MG with thymoma is most common between the ages of 40 and 60 years. Men predominate in the over-60 age group, whereas women outnumber men 3:1 in the under-40 age group.

Symptoms and signs

The clinical hallmark of MG is painless fluctuating skeletal muscle weakness that worsens with exercise and improves with rest. There is a characteristic diurnal pattern of weakness, gradually worsening throughout the day and improving with rest or sleep. Some individuals find that symptoms improve in a cold ambient temperature.

Any skeletal muscle may be affected in MG, but certain muscles and muscle groups are especially susceptible, notably those supplied by the motor cranial nerves. More than 90% of patients have peri- and extraocular muscle involvement, with ptosis and diplopia being common symptoms. Typically there is asymmetric weakness of several muscles of both eyes accompanied by weakness of eye closure. Eye movements resembling internuclear ophthalmolegia (pseudo-INO) and one-and-a-half syndrome (pseudo-one-and-a-half syndrome) are described. Patients often attempt to correct partial ptosis by contracting the frontalis muscle, causing a characteristic wrinkled brow appearance. Repeated blinking causing diagnostic confusion with blepharospasm has been reported.[3] A twitching of the upper eyelid seen a moment after the eyes are moved from downgaze to the primary position, Cogan's lid twitch sign, is said to be a characteristic sign of ocular myasthenia, but sensitivity and specificity are relatively low, as it may be seen in other oculomotor brainstem disorders.[4] In 15–20% of patients, weakness is confined to the ocular muscles, ocular MG, whereas others present with or will develop the generalized form of MG.

The muscles of facial expression, mastication, swallowing and speech are the next most commonly affected group. Relatives may notice that a lack of facial movement makes the patient look depressed and that the smile has a transverse or snarling quality ('myasthenic snarl'). Jaw weakness may interfere with chewing; in extreme cases, the jaw hangs open and has to be supported by the patient's hand. Palatal weakness can result in dysarthria with a nasal quality and in reflux of liquids through the nose when drinking.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Dysphagia and choking reflect involvement of pharyngeal and tongue musculature and hoarseness and dysphonia caused by laryngeal weakness are frequently seen.

Neck muscle weakness is common and the head may droop forwards in severe cases; MG is one of the most common causes of the 'dropped head syndrome'.[5] In generalized MG, the proximal limb muscles are typically most affected, but predominantly distal[6] and sometimes very focal weakness are described.[7] Tendon reflexes are normal or brisk and sensation is intact.

Clinical examination should pay particular attention to shoulder abduction, elbow extension, wrist and finger extension, finger abduction and hip extension, as these are frequently weaker and fatigue more quickly than their antagonistic limb movements. In severe cases, all muscles can be involved, including the diaphragm and intercostal muscles, causing dyspnoea and hypoventilation. Muscle wasting may be seen on occasion in chronic, poorly controlled disease. Muscle strength should be quantified (MRC grading) as serial assessment may give an objective early warning of deterioration, and also help to monitor treatment efficacy. Measurements should include vital capacity (VC), timed elevation of the eyes and eyelids and forward abduction of the arms. A rapid decline in VC or a reading below 1 l are signs of imminent respiratory failure.

Muscle weakness can be worsened by a wide range of conditions, including intercurrent diseases, especially infections, fever, extremes of temperature and emotional upset. In addition, many drugs may adversely affect myasthenia[8] and should be used with caution in poorly controlled patients (Table 66.1). If possible, neuromuscular blocking agents should not be used during general anaesthesia. Sufficient muscle relaxation can usually be provided by inhalation anaesthetics alone. Many other drugs may increase weakness and it is a useful rule to monitor carefully all MG patients when starting a drug that is new to them.

Whether cardiac function is impaired in MG remains uncertain. Although there is no evidence for an increased risk of heart-related deaths, there may be subclinical alterations in cardiac function in some MG patients, possibly related to the autoimmune diathesis and reversible with acetylcholinesterase inhibitors. Focal myocarditis and non-specific myocardial changes have been reported in pathological series, especially in MG associated with thymoma.[9]

A central cholinergic deficit in MG, commensurate with that at the neuromuscular junction, has been suggested, with resulting impaired memory function (cholinergic deficits are thought to be important in both Alzheimer's disease and dementia with Lewy bodies). Some studies have suggested cognitive impairments in MG patients, some of which improve with immunotherapy, but others have found no evidence for such impairments in MG patients compared with normal controls and hence no support for the idea of impaired central cholinergic mechanisms.[10]

Table 66.1 Drugs that may worsen MG.

Neuromuscular blockers, including D-tubocurarine, pancuronium, curare and succinylcholine
Aminoglycosides, including gentamicin, streptomycin, kanamycin, neomycin and viomycin
Polymixins, including polymixin B and colistin
Beta-blockers
Calcium channel antagonists
Quinine, quinidine and procainamide
Chloroquine and hydroxychloroquine

Penicillamine-associated myasthenia gravis

Unlike the many drugs that may temporarily worsen MG, D-penicillamine may induce immune-mediated MG. Typically the disease is mild, often ocular, associated with the transient production of low-titre AChR antibodies in patients who are HLA Bw35 DR1 positive, responds to acetylcholinesterases and remits permanently within months of stopping D-penicillamine. However, clinical, genetic and immunological heterogeneity are reported, as in spontaneous MG, with occasional patients developing severe and persistent seropositive or seronegative MG requiring ongoing immunotherapy.[11]

Diagnostic investigations: bedside

The distinctive clinical picture may enable a confident diagnosis of MG to be made, but additional investigations are desirable since there is a differential diagnosis (see below). Diagnostic confusion arises most frequently when MG is mild or when one of the clinical features dominates the presentation. Patients may not volunteer a history of fluctuating weakness and it is useful to ask about this, particularly diurnal variability with sleep benefit, in anyone presenting with tiredness, ptosis, diplopia, dysphagia or hoarseness. Examination should include assessment of muscle power and fatigability with repetitive contraction. Even when symptoms are restricted to one area, it is sometimes possible to demonstrate weakness in the typical pattern described above.

Anticholinesterase (Tensilon) test

Although this is the least specific of the standard tests for MG, it is frequently used because it is relatively easy

to perform at the bedside and provides an immediate result, whereas other tests and their results (blood tests, neurophysiology) may be delayed.

Edrophonium chloride (Tensilon) is a short-acting acetylcholinesterase inhibitor. A test dose of 1–2 mg is given through an intravenous cannula, a further 5–8 mg being given if there is no adverse reaction. The test is positive if muscle strength improves within 1 min. Assessment should be as objective as possible and include VC measurement and forward elevation of the arms, in addition to monitoring of ptosis and diplopia. Increased muscle power lasts for about 5 min. Some patients may develop a severe bradycardia and occasionally ventricular fibrillation. Pretreatment with i.v. atropine (0.6 mg) is probably advisable and the test is best performed with ECG monitoring and definitely with resuscitation equipment discreetly to hand.

Positive responses to the Tensilon test may occur in a wide range of conditions, including LEMS, motor neurone disease, neuropathies, myopathies and even psychogenic weakness and intracranial tumours. This test is probably best reserved for the situation where there is a strong clinical suspicion of MG but the results of antibody tests are negative or not yet available and EMG is awaited.

Ice pack test

The 'ice pack test' or 'ice on eyes' test has been proposed as a useful method of distinguishing ptosis due to MG from other causes. An ice cube is applied to the ptotic eyelid for at least 2 min and the response noted: improvement in ptosis (>2 mm, positive response) is both sensitive and specific for the diagnosis of myasthenia and correlates with the result of the Tensilon test, although false negatives have been described.[12] Pooling of results from six studies ($n = 76$ MG patients, $n = 77$ patients with non-myasthenic ptosis) gave a test sensitivity of 89%, a specificity of 100% and positive and negative predictive values of 100 and 91%, respectively, for the ice pack test.[12] Utility of the ice pack test in the assessment of extraocular muscle weakness remains to be shown.[13]

Compared with AChR antibody assay and neurophysiological testing, the ice pack test has the advantages of being cheap, quick and not requiring specialist equipment. Moreover, compared with the Tensilon test, no specialist medications are required, it is free of adverse effects and its result, although not unequivocal, is usually easy to interpret.[12]

Sleep test

That rest improves myasthenic ptosis is widely observed. A standardized 'sleep test' or 'rest test' has been advocated for the diagnosis of MG, a positive result being resolution of ptosis or ophthalmoparesis after 30 min of sleep.[14]

Diagnostic investigations: laboratory

Laboratory tests are essential to confirm the diagnosis, as treatment may involve surgery and drug therapy with potentially serious adverse effects.

Acetylcholine receptor (AChR) antibodies

The autoimmune nature of MG was first suggested by Simpson in 1960,[15] the evidence for which is summarized in Table 66.2. The most specific blood test for MG is the presence of serum AChR IgG antibodies detected by radioimmunoprecipitation assay (RIA). This uses AChRs labelled with an iodinated toxin that binds specifically to these receptors. False positives are rare in the healthy British population, including the elderly, although 7% of a group of patients over the age of 65 years selected for their predisposition to autoimmune disease (assessed by raised antithyroid antibody titres) had raised levels. The assay does not detect AChR antibodies in patients with seronegative MG.

Anti-MuSK antibodies

About 10–50% of MG patients without AChR antibodies have antibodies directed to the muscle-specific receptor tyrosine kinase MuSK.[16] MuSK mediates the agrin-induced

Table 66.2 Evidence that MG is an antibody-mediated autoimmune disease.

Antibody can be demonstrated in the majority of patients with the disease: AChR antibodies are detected in 85% of patients with generalized MG
Passive transfer of the antibody to experimental animals reproduces the disease: IgG from myasthenics injected into mice induces the clinical and electrophysiological features of MG
Antibody interacts with the target antigen: electron microscope immunohistochemistry has shown that AChR antibodies, in addition to complement, localize to postsynaptic structures in a pattern appropriate to affect AChRs in a destructive autoimmune process
Immunization with antigen produces a model of the disease: animals immunized with purified AChR develop myasthenia
Lowering serum antibodies improves the disease: removal of circulating antibodies by plasma exchange results in marked, but transient, improvement in disease in most myasthenics. After treatment, the antibody titre rises and the weakness returns

clustering of AChRs during synapse formation and is also expressed at the mature neuromuscular junction. MG with MuSK antibodies is often associated clinically with persistent bulbar involvement, including marked facial weakness involving buccinators, orbicularis oris and orbicularis oculi and tongue muscle wasting and respiratory crises.[17]

Striated muscle and other antibodies

Antibodies that bind to components of striated muscle cell membrane are found in 30% of all MG patients and in 70–90% of those with a thymoma. Therefore, anti-striated muscle antibodies may be used as a serum marker for this tumour. In addition, subgroups of these antibodies reacting with titin or ryanodine receptors are particularly associated with severe MG and also with thymoma. Antibodies that react with myosin, α-actin, actinin, β-adrenergic receptors and muscarinic AChR have also been demonstrated in MG, but their pathophysiological significance, if any, remains unclear.

Neurophysiology: electromyography

The most commonly used neurophysiological tests are repetitive nerve stimulation (RNS) and single-fibre electromyography (SF-EMG). Results may be misleading in patients who have been on chronic high-dose anticholinesterase treatment because of drug-induced downregulation of AChRs. If there is any doubt about EMG findings, it is better, if possible, to stop these drugs for 1 week and then repeat the tests.

In RNS, a train of electric stimuli at 3–5 Hz is given to a nerve and compound action potentials are recorded from the relevant muscle. A decline in the amplitude of the fifth compared with the first potential of more than 10% (decrementing response) is judged positive. This is found in about 50% of mild MG patients and 80% of those with more severe weakness.

During SF-EMG, recordings are made from two or three different muscle fibres within a single motor unit. The finding of increased jitter, a breakdown in the timing relationship of activation between the muscle fibres, often accompanied by blocking of successive muscle discharges, is abnormal. When recordings are made from a range of muscles, abnormal responses are seen in up to 99% of generalized MG patients and 84% of those with pure ocular disease. This test is therefore highly sensitive. However, these findings are not specific, since jitter and blocking can occur in LEMS and in conditions where there is reduced muscle fibre density, such as motor neurone disease. Furthermore, SF-EMG can be difficult to interpret in elderly patients as jitter increases with age and normal values were established in individuals under the age of 60 years.

Table 66.3 Immune disorders reported in association with MG.

Thyroid disease: both hyper- and hypothyroidism
Rheumatoid arthritis
Systemic lupus erythematosus
Acquired peripheral nerve hyperexcitability (neuromyotonia)
Sjögren syndrome
Polymyositis
Selective or pan-hypogammaglobulinaemia
LEMS
Dermatological diseases: pemphigus, lichen planus, vitiligo, alopecia
Haematological disease: pernicious anaemia, red cell aplasia, neutropenia, aplastic anaemia, idiopathic thrombocytopenic purpura

Imaging

Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan of the mediastinum should be obtained to look for thymoma. In those at high risk (raised AChR and striated muscle antibody titres), a negative scan should prompt re-imaging after 2–3 years.

Other tests

In all patients it is advisable to look for evidence of other autoimmune disorders, especially thyroid (Table 66.3). In difficult cases, specialist techniques are available, including muscle biopsy for quantification of endplate AChRs and immunohistological and electrophysiological studies.

Differential diagnosis

A number of conditions can mimic (seronegative) MG and cause diagnostic confusion, including LEMS, certain restricted myopathies, mitochondrial cytopathies especially with the chronic progressive external ophthalmoplegia (CPEO) phenotype, motor neurone disease, peripheral neuropathies, hyperthyroidism and psychogenic weakness. Intracranial mass lesions, including brainstem glioma and giant vertebrobasilar aneurysm, have been reported to present as 'MG' on occasion.

Clinical classification of MG and associated diseases

The progression of MG is variable and it is difficult to predict the outcome in an individual patient. However, the classification shown in Table 66.4, the Myasthenia Gravis Foundation of America grades,[18] serves as an aid both to prognosis and to planning of treatment, although some atypical cases sit uneasily within the classification.[7] Based on this, studies have established several useful clinical

Table 66.4 Clinical classification of MG.

Group 1	Ocular myasthenia
Group 2A	Mild generalized myasthenia with slow progression
Group 2B	Moderate generalized myasthenia with prominent bulbar involvement
Group 3	Acute fulminating myasthenia with rapid progression and respiratory crises
Group 4	Late severe myasthenia similar to group 3, but starting as group 1 and progressing in less than 2 years to become generalized

guidelines.[19] Only 10–15% of patients with MG limited to the ocular muscles for 2 years will progress to develop generalized disease. In generalized MG, the rate of progression is more variable. However, maximum severity is reached within the first year in two-thirds of patients and respiratory crises are more likely to develop with increasing age of onset. Typically, MG follows a chronic course. Spontaneous remissions occur in less than half of all patients and are usually temporary.

Autoimmune diseases tend to cluster both in individuals and in families. Hyperthyroidism, rheumatoid arthritis, PNH and systemic lupus erythematosus are the diseases most consistently reported in association with MG (Table 66.3).

Is MG different in the elderly?

Could the underdiagnosis of MG in the elderly[2] be ascribed, at least in part, to the disorder being in some ways different in this age group? Certainly the disorder is more common in men than women over the age of 60 years and thymoma is more common in the older age group. It has also been argued that the typical clinical features of MG may be more difficult to spot in older individuals, since age-related decrease in total eyelid area with sagging of the lower eyelids makes ptosis less easy to diagnose and diplopia may not be detected due to impaired vision from macular degeneration or cataract formation. The mean concentration of AChR antibodies is lower in elderly MG patients but seronegative MG is less common. Antibodies to titin are found in ~30% of patients with late-onset nonthymoma MG, but these antibodies are extremely rare in early-onset MG.[20] Use of steroids and immunosuppressive agents for the treatment of the elderly MG patient may pose greater risks of adverse effects, for example with steroid-induced osteoporosis, hence the need for prophylactic treatment.

Management

The management of MG varies with the type and severity of the disease, individual disease progression, concurrent illness, age of the patient and experience and familiarity of the treating physician with a particular treatment regime. Anticholinesterases, immunosuppressants, plasma exchange (PE), intravenous immunoglobulin (IVIG) and thymectomy are the most frequently used therapies (Figure 66.1).[19] Current treatment strategies result in at least 90% remission or substantial improvement leading to a good quality of life.

Anticholinesterase inhibitors

These are the first-line drugs for all MG patients and act by inhibiting acetylcholine breakdown at the NMJ.[19] They are used to provide long-term symptomatic improvement in mild disease, especially ocular, and as temporary adjunctive therapy in patients embarking on definitive treatment. They act within 10–30 min, have a maximum effect at 2 h and their effects last for about 4 h. The starting dose of pyridostigmine, the most widely used drug, should be 30 mg two to four times per day, gradually increasing according to response, usually up to a dose of 60 mg five times a day.

High doses will produce more adverse effects. The common muscarinic adverse effects include abdominal cramps, diarrhoea, increased sweating and excessive bronchial and oral secretions. Propantheline can alleviate these problems, but may mask the signs of overdose. The main nicotinic adverse effects are muscle fasciculations and cramps. Chronic high doses may increase weakness by downregulating AChRs. Pyridostigmine should be slowly withdrawn when immunosuppressive treatment has been established or after thymectomy.

Steroids

Steroids are useful as short-term immunosuppressants in MG.[21] They are used as an interim measure while titrating up the doses of other immunosuppressants and waiting for them to be effective. Some patients experience a temporary worsening of MG if steroids are started at high doses. This 'steroid dip' usually occurs 4–10 days after starting steroids. To overcome this problem, alternate day treatment has been shown to be effective. Oral prednisolone, the recommended first-choice drug, should be started at a low dose of 10 mg on alternate days, gradually increasing by 10 mg per dose to 60–80 mg on alternate days. Improvement usually occurs within 1–4 weeks. Owing to the adverse effects of prolonged steroid use, when remission occurs, the dose should be slowly reduced to the minimum effective dose, given on alternate days. In critically ill patients, high-dose daily steroids may be started and additional short-term treatments such as intravenous immunoglobulin and plasma exchange can be used to overcome any temporary worsening of MG.

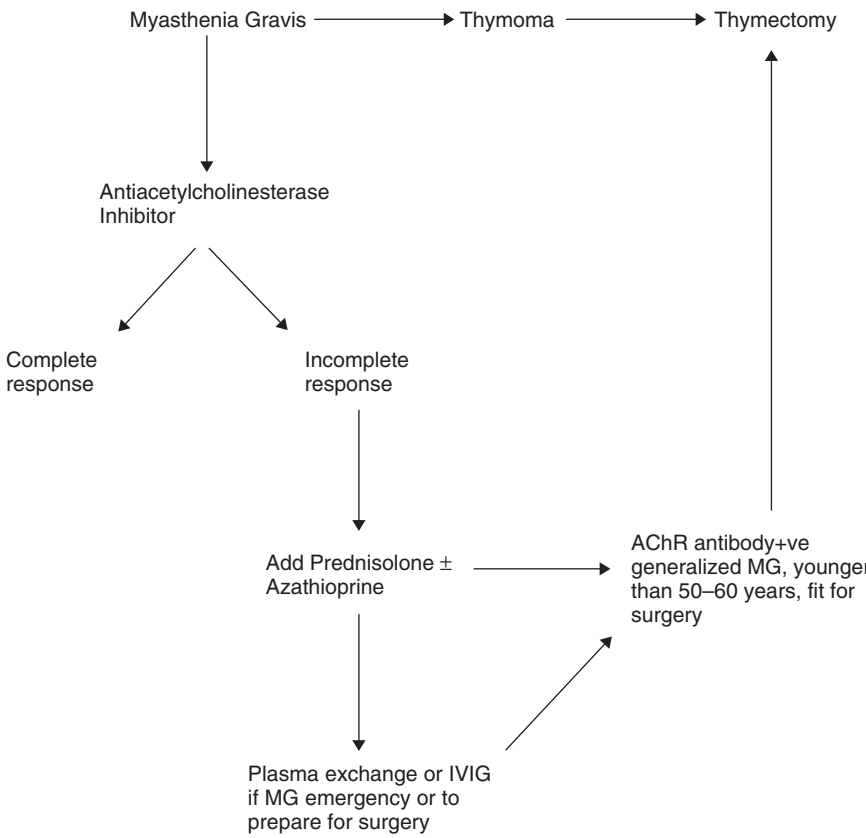

Figure 66.1 An algorithm for the management of MG.

Long-term steroid use is associated with many adverse effects, including cushingoid features, infections, hypertension, diabetes mellitus, osteoporosis, psychiatric disorders, insomnia and elevations in white cell count. It is worth highlighting that it is now routine to cover steroid treatment with a prophylactic bisphosphonate.

Long-term immunosuppressants

In many countries, azathioprine is the first-choice long-term immunosuppressant. It is usually used in combination with steroids to allow tapering of steroids to the lowest dose possible.[21] It has the disadvantage that treatment must often be continued for 6 months to 2 years before maximum clinical improvement is seen. Azathioprine is typically started at 50 mg per day and the dose is increased by 50 mg per week until a maintenance dose of 2.5 mg kg^{-1} is reached. After remission, the dose is slowly reduced by 25–50 mg per month provided that full control of symptoms is maintained. When used in combination with prednisolone, the steroid is withdrawn first.

Common adverse effects include hepatotoxicity, nausea, vomiting, rash, cytopenia and pancreatitis. In the long term, malignancy is a potential complication, but the absolute risk is difficult to evaluate because of the problem of separating the effects of the drug from age-related increases in the background incidence of cancer. Most patients tolerate the drug well and mild but stable haematological or liver-related blood test abnormalities without symptoms are not usually reasons for stopping treatment. Full blood count and liver-related blood tests must be monitored weekly for the first 8 weeks of therapy and 3 monthly thereafter. If there are progressive blood test abnormalities, the drug must be stopped, although it is often possible to restart treatment at a lower dose after the blood tests have returned to normal.

Several guidelines have suggested that methotrexate should be used as a second-line immunosuppressant in MG.[19,21] The adverse effects are usually mild (e.g. alopecia, gastrointestinal intolerance, mild abnormalities of liver-related blood tests, mucositis), although severe adverse events such as haematopoietic suppression, hepatotoxicity and pneumonitis can sometimes occur. Mycophenolate mofetil and tacrolimus should be considered in patients who are intolerant of or unresponsive to azathioprine or methotrexate.[21] Mycophenolate mofetil in particular appears to be well tolerated and has a relatively good adverse effect profile.[22] Ciclosporin and cyclophosphamide should only be considered if other immunosuppressants fail, as these drugs can cause serious adverse effects.[21]

Plasma exchange

In most MG patients, weakness improves after PE.[23] It is thought to act mainly by removing circulating antibodies. A standard protocol is five exchanges each of 50 ml kg^{-1} body weight over 5–7 days. Improvement typically begins within 1–2 days, is maximal at 1–2 weeks and lasts about 1–3 months. It is mainly used to treat myasthenic crises and for rapid stabilization of patients undergoing thymectomy. Prethymectomy PE improves outcome after thymectomy in MG. Most adverse effects are related to issues of vascular access such as infection, thrombosis, pneumothorax and, rarely, air embolism. Excessive fluid volume shifts can cause fluid overload and congestive heart failure or hypotension. Citrate infused for anticoagulation may lead to hypocalcaemia and disturbances in acid–base homeostasis.

Intravenous immunoglobulin

The indications for IVIG in MG are the same as those for PE.[23] Improvement is seen in most patients within 4–5 days and lasts from several weeks to several months. Typically, 0.4 g kg^{-1} body weight is given daily for 5 days. The mode of action of IVIG in MG is incompletely understood. Common adverse effects include fever, headache, nausea and allergic reactions. A severe anaphylactic reaction might occur in patients with IgA deficiency. Volume overload may occur in cardiomyopathy and solute-induced renal failure may occur in patients with pre-existing renal compromise. High infusion rates may cause thrombosis and stroke. However, the adverse effects from IVIG appear less severe than those from PE.

Thymectomy

This is the treatment of choice for a thymoma if there are no anaesthetic or medical contraindications.[24] If the patient is unfit, radiotherapy may be indicated. When MG is associated with a thymoma, the disease may be more aggressive, requiring the use of immunosuppressants in most patients following thymectomy. In non-thymoma patients, thymectomy is usually performed in patients with generalized MG, younger than 50–60 years of age and positive for AChR antibodies.[24] Although thymectomy has been used since the 1940s, pioneered in the UK by Sir Geoffrey Keynes, clinical trials have not been undertaken. An international trial comparing thymectomy plus steroid treatment versus steroid treatment alone is currently under way.[25] The most common surgical techniques performed are extended trans-sternal thymectomy and video-assisted endoscopic thymectomy, although the debate on which is better is ongoing.

The clinical benefit from a thymectomy may only become apparent 6–12 months after surgery. Factors associated with a good response to thymectomy include female gender, predominance of weakness affecting limb muscles and the presence of AChR antibodies.

Management in special circumstances

In pure ocular myasthenia, most patients do not respond adequately to pyridostigmine alone and prednisolone is needed.[24] Prednisolone is usually started at a low 10 mg alternate day dose, gradually increasing, as described above, to a maximum of 20–40 mg on alternate days. The diagnosis of ocular myasthenia needs to be re-evaluated if there is an absolute lack of response after 3 months. In patients with only partial response to steroids, a long-term immunosuppressant such as azathioprine needs to be considered.

Myasthenic and cholinergic crises are said to occur if weakness is severe enough for a patient to require ventilation. Myasthenic crisis is usually precipitated by infection or other intercurrent disease, surgery or too rapid a decrease in immunotherapy doses. Excessive treatment with anticholinesterase inhibitors causes the rarer cholinergic crisis. It can be difficult to distinguish between the two types of crisis. If in doubt, it is safe to stop the anticholinesterase inhibitors once the patient is on a ventilator. Infection, if present, must be aggressively treated. In myasthenic crises, IVIG or PE is usually indicated and the doses of immunosuppressants may be increased as appropriate.

When an MG patient requires anaesthesia, the local or spinal route is preferred if possible. If a general anaesthetic is required, a nasotracheal tube is inserted at operation to allow ventilation to be assisted postoperatively if needed. The tube is kept in for 1–2 days, by which time the VC usually recovers sufficiently to allow extubation. Anticholinesterase inhibitors increase bronchial secretions and are best avoided on the morning of the operation and for 24 h afterwards. Immunosuppressant drugs should be continued.

Lambert–Eaton myasthenic syndrome

The experimental approaches first used in MG, focusing on the criteria listed in Table 66.2, have established LEMS as the second antibody-mediated autoimmune disorder of neuromuscular transmission. Presynaptic motor nerve terminal voltage-gated calcium channels (VGCCs) are the main antigenic targets. LEMS may be divided into two types: paraneoplastic, occurring as a remote effect of a neoplasm, and spontaneous. Two-thirds of patients, mainly older male smokers, develop LEMS in association with a tumour, most commonly small cell lung carcinoma (SCLC) and more rarely lymphoma, certain adenocarcinomas and thymoma.[26] It is thought that VGCCs on tumour cells trigger the production of antibodies that cross-react with

antigenically similar nerve channels and that this leads to channel downregulation and a reduction in transmitter release. Spontaneous cases tend to be younger, have no smoking history and are usually women. About 3% of those with SCLC develop LEMS and the overall incidence is about 4 per million.

In the typical case,[27] LEMS most often presents with subacute ascending weakness of the proximal limb muscles, typically affecting the lower limbs first and causing a characteristic rolling gait. Ptosis and diplopia can occur. Bulbar and respiratory muscle weakness are much less common than in MG. Features of autonomic dysfunction are frequently found, including dry mouth (xerostomia), constipation, urinary hesitancy and impotence. Some patients complain of paraesthesias and muscle aches. On examination, the strength of the affected muscles can increase during the first few seconds of a maximal voluntary contraction, a phenomenon known as augmentation. Tendon reflexes are typically reduced or absent, although may be transiently restored to normal after 15–30 s of sustained muscle contraction, a phenomenon known as post-tetanic potentiation or facilitation. The course of LEMS is variably progressive.

The syndrome, most frequently the spontaneous form, is associated with other autoimmune diseases, including vitiligo, thyroid disorders, diabetes mellitus and pernicious anaemia.[26] Paraneoplastic LEMS may coexist with other paraneoplastic neurological syndromes, including subacute cerebellar degeneration and encephalomyelitis. Serum VGCC IgG antibodies to the P/Q subtype of channels are detected in up to 90% of patients with paraneoplastic LEMS and 76% of those with the spontaneous disease by an RIA using [^{125}I]-ω-conotoxin MVIIC, which binds specifically to these channels. On EMG, typically there is a marked reduction in the amplitude of the compound muscle action potential following supramaximal nerve stimulation, that increases following maximal voluntary contraction for 15 s. A 25% increase in amplitude is suggestive of LEMS and a 100% increase is diagnostic. On single fibre recordings, increased jitter with frequent blocking may be found, as in MG. Nerve conduction studies are normal. Patients may respond to edrophonium but not as dramatically as those with MG. Repeated screening tests for tumours should be carried out particularly in those patients with a high risk of malignancy such as smokers, as SCLC may not be obvious for up to 5 years after onset of LEMS. Whole-body positron emission tomographic (PET) imaging may have a role in detecting occult tumours in paraneoplastic syndromes.

The definitive management of paraneoplastic LEMS is treatment of the tumour. This often leads to neurological improvement.[19] In those cases of LEMS with tumour or at high risk of developing one, the first-line drug treatment is 3,4-diaminopyridine (10–20 mg up to five times per day), a potassium channel inhibitor that increases acetylcholine release from neurons. Side effects include perioral and other paraesthesias. Sometimes the addition of pyridostigmine produces a further small improvement in muscle strength.

Mild cases of spontaneous LEMS are also treated with these drugs. Severe weakness requires the addition of immunosuppressive agents. The combination of prednisolone (1–1.5 mg kg^{-1} body weight) and azathioprine (2.5 mg kg^{-1} body weight) seems to be the most effective and the treatment plan generally follows that for MG. However, the response is slower, improvement may be delayed for 6 months and after stabilization immunosuppressive drugs can rarely be withdrawn completely. Prednisolone may be useful in paraneoplastic LEMS when weakness fails to respond well to treatment of the tumour.

Patients may improve temporarily after plasma exchange and this can be used to supplement other treatments. Similarly, IVIG can increase muscle strength, mirrored by a decline in anti-VGCC antibody titres. Improvement lasts from 4 to 6 weeks.

Peripheral nerve hyperexcitability

The most common acquired clinical variant of generalized PNH is neuromyotonia (Isaacs syndrome) caused by antibodies to neuronal voltage-gated potassium channels (VGKC). This is a rare and heterogeneous syndrome characterized clinically by complaints of muscle stiffness, cramps, twitching, weakness and delayed muscle relaxation (pseudomyotonia). Symptoms are often triggered by muscle contraction and disability can be severe. About one-third of patients have some sensory features such as paraesthesias and central nervous system features can occur (Morvan syndrome). There is neurophysiological evidence of continuous motor unit activity of peripheral nerve origin. Spontaneous firing of single motor units as doublet, triplet or multiplet discharges with high intraburst frequency (40–300 per second) at irregular intervals is the hallmark finding. The persistence of these findings after proximal nerve blockade with local anaesthetic agents proves their peripheral nerve origin, suggesting that the discharges arise in the terminal arborizations of motor nerves.[28,29]

Neuromyotonia is paraneoplastic in up to 25% of patients and can predate tumour detection by up to 4 years, thymus and lung being the typical underlying tumours. There is no autoantibody that indicates whether PNH is paraneoplastic. VGKC antibodies are found in about 35% of all PNH patients, rising to 80% in those with thymoma. A paraneoplastic syndrome of limbic encephalitis complicated by epileptic seizures and hyponatraemia may also be

associated with VGKC antibodies, with or without clinical evidence of PNH.[30]

All forms of neuromyotonia usually improve with symptomatic treatment. Suitable agents include carbamazepine, phenytoin, lamotrigine and sodium valproate, in combination if necessary. Paraneoplastic neuromyotonia often improves and may remit after treatment of the underlying tumour. Immunomodulatory therapies may be considered in patients with likely autoimmune variants of PNH with debilitating symptoms which are refractory to symptomatic treatments. Plasma exchange often produces useful clinical improvement lasting about 6 weeks accompanied by a reduction in EMG activity and a fall in VGKC antibody titres.[29] Case studies suggest that IVIG may also be helpful. By analogy with LEMS, selected patients with severe neuromyotonia refractory to other treatments may benefit from serial immunomodulatory therapy every 6–8 weeks. There are no good trials of long-term oral immunosuppression. However, prednisolone with or without azathioprine or methotrexate has been useful in selected patients.[19]

Acknowledgement

This chapter is dedicated to our friend and colleague Dr Ian Kirkland Hart, who died suddenly on 10 November 2008, and is based upon his chapter in the previous (4th) edition of this textbook, published in 2006.

Key points

- MG, LEMS and PNH are all antibody-mediated NMJ disorders.
- MG incidence rises with age but is underdiagnosed in the elderly.
- MG is treatable, with more than 90% of patients returning to normal function, so the diagnosis should be considered in anyone presenting with ptosis, diplopia, dysphagia, limb or respiratory muscle weakness.

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CHAPTER 67

Muscle disorders

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Introduction

Myopathies may be inherited or acquired. Although the latter are more common in geriatric practice, several inherited myopathies may present for the first time in middle age or later and may raise genetic issues for other family members. The acquired myopathies, with a few notable exceptions, often recover with appropriate management. For all of the conditions that are discussed in this chapter, appropriate support, even in the absence of specific therapy, will help improve quality of life and reduce morbidity.

The clinical features of myopathies are relatively limited and include weakness and muscle wasting, fatigue, pain, tenderness, myotonia and muscle twitching. At the bedside it may be impossible to decide whether weakness and wasting are due to a myopathy or a neurogenic disorder. Thus, the differential diagnosis of myopathy includes anterior horn cell disorders (e.g. amyotrophic lateral sclerosis and spinal muscular atrophy), nerve root and plexus disorders, peripheral neuropathies and myasthenic disorders. The presence of upper motor neurone signs and sensory symptoms and signs clearly suggests a more proximal cause of problems than skeletal muscle, but in their absence it is important not to forget that weakness alone is often due to nerve rather than muscle disease. The role of laboratory investigations in helping to distinguish between neurogenic and myopathic diseases is discussed below.

There are several ways of approaching the classification of muscle disorders. For example, inherited disorders can be classified by phenotype or by gene/protein product. For everyday usage, a subdivision into acquired and inherited disorders is useful (Tables 67.1 and 67.2). In the elderly (Table 67.3), the most frequently encountered disorders are the idiopathic inflammatory myopathies, drug-induced myopathies and muscle disease in association with endocrine and metabolic disease.

Table 67.1 Acquired myopathies.

Idiopathic inflammatory myopathies
– Polymyositis
– Dermatomyositis
– Inclusion body myositis
– Myositis associated with connective tissue disorders
Toxic
– Alcohol
– Drugs
Endocrine and metabolic
– Acromegaly
– Hypothyroidism
– Hyperthyroidism
– Cushing syndrome
– Addison disease
– Disorders of vitamin D and calcium metabolism
Infection
– Viral
– Bacterial
– Parasitic
Paraneoplastic myopathies

Clinical assessment

The patient's history is likely to be more revealing than physical examination, although laboratory investigations may be required to establish the precise diagnosis.[1,2] In the history, particular attention must be paid to determining the site of onset and rate of progression of skeletal muscle involvement and the presence of associated symptoms such as muscle wasting and pain. There must be a detailed recording of the family history and drug history. For myopathies secondary to systemic disease (Table 67.1), the underlying cause may be identified from the history and physical examination. In practice, the most frequently encountered pattern of skeletal muscle involvement is that of painless proximal weakness affecting the pelvic girdle

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 67.2 Inherited myopathies.

Muscular dystrophies
– (See Table 67.8)
Myotonic dystrophies
Congenital myopathies
– Central core disease
– Nemaline myopathy
– Myotubular/centronuclear myopathy
– Multi-mini-core disease
Metabolic myopathies
– Glycogenosis (e.g. McArdle syndrome)
– Lipid disorders (e.g. disorders of fatty acid β-oxidation)
– Mitochondrial cytopathies
Channelopathies
– Sodium (hyperkalaemic periodic paralysis, paramyotonia congenita)
– Calcium (hypokalaemic periodic paralysis)
– Chloride (myotonia congenita)
– Ryanodine receptor (malignant hyperthermia, core diseases)

Table 67.3 Major myopathies in the elderly.

Idiopathic inflammatory myopathies
Toxic myopathies
Endocrine and metabolic myopathies
Oculopharyngeal muscular dystrophy
Mitochondrial chronic progressive external ophthalmoplegia

more than the shoulder girdle. In the acquired myopathies (Table 67.1), onset may be acute or chronic, whereas in the inherited myopathies (Table 67.2), progression is usually slow. Asymmetric involvement is uncommon but may be a striking feature in inclusion body myositis (IBM) and facioscapulohumeral (FSH) muscular dystrophy. Early involvement of distal muscles is seen in myotonic dystrophy and IBM.

There is early involvement of the extraocular muscles (causing ptosis and/or ophthalmoplegia) in myasthenia gravis, mitochondrial cytopathies, Graves' ophthalmopathy and oculopharyngeal muscular dystrophy. Ptosis and facial weakness are seen in myotonic dystrophy and facial weakness is a particular feature of FSH muscular dystrophy and some of the congenital myopathies. Myasthenia gravis most frequently presents with intermittent diplopia and ptosis. Subsequently there may be facial and bulbar muscle involvement.

Weak muscles eventually become wasted, but in many myopathies the bulk is maintained for a long time, whereas in neuropathies wasting is generally an earlier feature. The tendon reflexes also tend to be lost early in neuropathies. Muscle hypertrophy is rare in acquired myopathies but is a feature of some of the muscular dystrophies (e.g. Duchenne/Becker dystrophy).

Respiratory muscle weakness may be asymptomatic, but evidence of it can be found on examination in the form of paradoxical abdominal movement. The best method of evaluation is by measurement of the forced vital capacity (FVC). In the presence of diaphragmatic weakness, the FVC falls when the patient lies down.

Most myopathies are painless at rest. Acute dermatomyositis (DM) may be painful, but rarely markedly so, and there is a striking difference between the modest pain and severe weakness seen in this condition and the severe pain and stiffness and absence of weakness seen in polymyalgia rheumatica. Aching is a common feature in hypothyroid myopathy and bone pain a major feature of osteomalacia. Acute drug-induced and acute alcoholic myopathies are often painful. Exercise-induced muscle pain is seen in several metabolic myopathies[1] and in Becker muscular dystrophy.

Clinical features alone usually provide a strong pointer toward the diagnosis and help determine the path of laboratory assessment.[3]

Laboratory investigations

A fairly common pathway from the clinical evaluation to diagnosis is via biochemical studies, electrophysiological assessment and muscle biopsy. For the inherited myopathies, this pathway is gradually being supplanted in part or in whole by specific DNA tests.[3]

Biochemical studies

Despite its lack of specificity, estimation of the serum creatine kinase (CK) is a useful marker for muscle disease. High levels are seen in Duchenne and Becker muscular dystrophy, acute drug-induced and toxic myopathies, inflammatory myopathies, some forms of limb-girdle muscular dystrophy and some metabolic myopathies. Levels are normal in many congenital myopathies, myotonic disorders, chronic drug-induced myopathies and many metabolic myopathies. Moderate elevation (up to 1000 i.u. l^{-1}) may be seen in anterior horn cell disorders. The serum aspartate aminotransferase (AST) level generally parallels the CK level in muscle disorders and not infrequently its elevation in the presence of otherwise normal liver function tests is the first indication of a myopathic disorder – however, this may not be appreciated and some patients undergo unnecessary liver investigations, including biopsy, before the penny drops and the CK is measured.

Dynamic studies (such as estimation of lactate generation during exercise and magnetic resonance spectroscopy) are of value in the investigation of suspected metabolic myopathies involving carbohydrate and mitochondrial metabolism and tandem mass spectrometry is of value in evaluating disorders of fatty acid β-oxidation.[1]

Electrophysiology

In primary disorders of the muscle, electromyography (EMG) characteristically shows a reduction in the size and duration of the motor unit potentials and an increase in the number of polyphasic units. Fibrillation potentials and positive sharp waves indicate muscle fibre irritability and are seen in inflammatory myopathies and some metabolic myopathies. Myotonic discharges are seen in myotonic dystrophy and myotonia congenita.

EMG may help in distinguishing between neurogenic and myopathic disorders, which may sometimes be difficult on clinical grounds alone.

Muscle biopsy

With the exception of DNA tests, muscle biopsy remains the single most powerful tool for the specific diagnosis of myopathies.[4] The muscle to be biopsied must be chosen with considerable care.[3] Tissue handling is extremely important and correct processing requires specialist facilities.[1] Biopsy findings in individual disorders are discussed throughout this chapter. Biopsy samples are also used for biochemical studies and mitochondrial DNA analysis.

Molecular studies

There has been rapid progress recently in the identification of the genetic basis of many of the inherited myopathies (see Gene Tables at http://www.musclegenetable.org/). This offers the prospect of rapid and precise diagnosis and the option of prenatal diagnosis. However, a number of practical difficulties remain in moving tests from the research arena to accredited diagnostic laboratories.[5]

Acquired myopathies

The acquired myopathies (Table 67.1) are of particular importance because many of them are either treatable or reversible. The idiopathic inflammatory myopathies are the subject of considerable research activity, which has aided classification and our understanding of pathogenetic mechanisms and is starting to help in determining therapeutic approaches. Toxic and drug-induced myopathies are seen at all ages but are particularly important in the elderly because of polypharmacy. Myopathy, occasionally severe, is common in many endocrine disorders and usually responds rapidly to correction of the underlying condition. Disorders of calcium and vitamin D metabolism in the elderly are an important cause of muscle weakness. Several forms of paraneoplastic myopathy exist but, in general, the condition is overdiagnosed.

Idiopathic inflammatory myopathies

Dermatomyositis (DM) and polymyositis (PM) share many clinical features and there are common approaches to treatment, but recent studies have shown that they have very different immunopathogenic mechanisms.[6] Inclusion body myositis may not be a true primary inflammatory myopathy but it is often confused clinically with PM and is particularly important in the present context because it is seen most frequently in the elderly.

Myositis may be seen in association with connective tissue disorders (including systemic lupus, scleroderma, Sjögren syndrome, rheumatoid arthritis and mixed connective tissue disease) and these are sometimes referred to as *overlap syndromes*.[6] Care must be taken to distinguish a true inflammatory myopathy as the cause of weakness in these conditions from other associated causes, such as peripheral neuropathy, muscle ischaemia, cachexia and drug-induced myopathy. Overall, clinically relevant inflammatory myopathy in these overlap syndromes is uncommon.

Dermatomyositis (DM) (see Chapter 125, skin disorders)

Clinical features

DM can develop at any age, is twice as common in females than males and has an annual incidence of about two per million population. Onset of weakness is usually subacute (weeks) but, in rare cases, has a more explosive onset with profound weakness, respiratory muscle involvement and rhabdomyolysis with myoglobinuria developing within a few days. Exercise-induced muscle pain and discomfort on palpation may be present but severe discomfort of the type associated with polymyalgia rheumatica is not seen. Dysphagia is common.

Clinical evidence of skin involvement is present in most, but not all, cases. The commonest features are a non-specific erythematous rash over the face and upper anterior chest wall (areas exposed to sunlight), a red–purple discoloration over the knuckles and dilatation of capillaries at the base of the nail bed (Figure 67.1). Characteristic, but seen less often, is a violaceous (heliotrope) discoloration of the eyelids. Raynaud's phenomenon, which may long predate the myopathy and arthralgia, is frequent. Interstitial pulmonary fibrosis may be asymptomatic, cause breathlessness and cough or occasionally be relentlessly progressive despite treatment and lead to death. There is an association between lung involvement and the presence of serum anti-Jo-1 antibodies. Cardiomyopathy and rhythm disturbances are underestimated and may also lead to death. In about 20% of cases overall, but more frequently in older patients, there is an association with carcinoma, but not with a particular carcinoma. Thorough clinical assessment is therefore

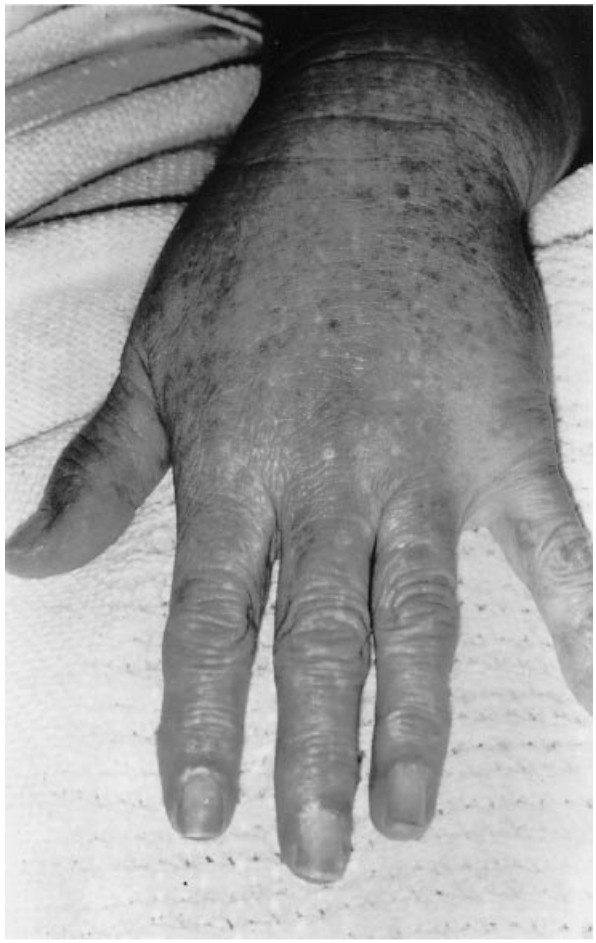

Figure 67.1 Dermatomyositis. Note erythema over knuckles and dilatation of the nail-bed capillaries.

essential, including rectal, vaginal and breast examination, sigmoidoscopy or more extensive endoscopy if there is a suggestive history, abdominal and chest scanning, testing for faecal occult blood and basic haematological and biochemical studies.[7] Positron emission tomography (PET) is becoming increasingly available as a screening tool to detect occult malignancy.

Diagnosis and pathological features

The serum CK is usually elevated and in acute cases the level may be very high. It is a useful but not absolute indicator of disease activity. The erythrocyte sedimentation rate (ESR) is normal in the majority of patients. Autoantibodies are frequently found but their identification is of little value with respect to diagnosis or prognosis, except perhaps for the association noted above between anti-Jo-1 and interstitial lung disease.[8] EMG shows an alteration in the motor unit potentials (reduced duration and an increase in polyphasic units) and electrical irritability (fibrillation potentials and positive sharp waves).

The diagnosis is confirmed by the muscle biopsy findings. Characteristic features include perifascicular atrophy, focal myofibrillar loss and areas of infarction. Vascular changes include capillary necrosis, undulating tubules in endothelial cells, arteriolar thrombosis and lytic membrane-attack complex deposition in vessel walls. Inflammatory infiltrates are typically found in septa and around blood vessels (Figure 67.2) and consist of B-lymphocytes, helper T-lymphocytes and plasma cells.

Pathogenesis

On the basis of the characteristic immunopathological muscle biopsy findings noted above, it is believed that DM is caused by humoral immune mechanisms which lead to destruction of capillaries and occlusion of arterioles. Muscle fibre damage is thus secondary to ischaemia. This contrasts with PM in which cell-mediated immune mechanisms lead to muscle fibre destruction.

Treatment

Knowledge of the natural history of DM is limited and there have been no completely satisfactory controlled trials of drug therapy. Prednisolone is the mainstay of treatment and a reasonable starting dose is $1\,mg\,kg^{-1}$ body weight per day. In severe cases, this may be preceded by intravenous methylprednisolone 500 mg daily for 5 days, although the evidence for additional benefit is lacking. Azathioprine ($2.5\,mg\,kg^{-1}$ body weight per day) or methotrexate (10–20 mg weekly) are widely used in combination with prednisolone, as long-term steroid-sparing agents. The steroid dose is maintained for 1–3 months (at least until the CK has returned to normal) and then lowered slowly at a rate determined by the clinical response and to a lesser extent by changes in the serum CK. A rise in the CK may precede exacerbation of weakness. As the disorder settles, the prednisolone can be changed to an alternate day regime, which may reduce steroid side effects. If the patient

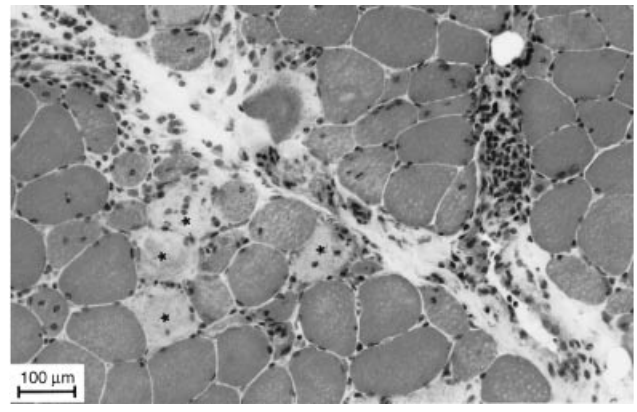

Figure 67.2 Dermatomyositis. Muscle biopsy (H&E, ×115). Note the perivascular inflammatory infiltrate and necrotic fibres (*).

does not respond to or cannot tolerate the above regime, then there are several other options. Alternative immunosuppressant drugs that are used (but without trial data) include mycophenolate mofetil and cyclophosphamide. Plasma exchange and leucapheresis appear to be ineffective. Intravenous immunoglobulin is almost certainly effective,[9] but there are insufficient data to recommend it over prednisolone as a mainstay of treatment, although it is fairly widely used in severe cases at first presentation together with high doses of steroids.

The cutaneous lesions respond to systemic steroid treatment. In the absence of significant muscle involvement, topical steroids may have a role. The skin is photosensitive and light-exposed areas should be treated with an ultraviolet blocking cream. Malnutrition (e.g. due to associated dysphagia) must be avoided to prevent muscle catabolism. Physical activity should be encouraged.

The prognosis with respect to muscle function and life expectancy is good if treatment is started early and there is no associated malignancy.

Polymyositis (PM)

Clinical features

Polymyositis is a disappearing disease as many cases previously diagnosed as PM have been reclassified as having IBM or myositis associated with connective tissue disease.[10] As in DM, the weakness is predominantly proximal but the onset is often insidious and the rate of progression slower. Muscle pain and tenderness are very uncommon. Elderly patients often give a history of deterioration of gait over 1–2 years, which is not infrequently attributed to arthritic hips.

Diagnosis and pathological features

The serum CK is usually elevated but may be normal in very slowly progressive or late stages of the disease. The ESR is unhelpful. Electromyographic changes are the same as those described for DM.

Muscle biopsy shows scattered necrotic and regenerating fibres. The vascular changes noted in DM are absent. Inflammatory infiltrates (Figure 67.3) tend to be within fascicles (endomysial) and are composed of cytotoxic T-lymphocytes and macrophages with fewer B-lymphocytes. A characteristic finding in PM, and also in IBM, is partial invasion of muscle fibres. Cytotoxic T-lymphocytes penetrate the basal lamina but not the muscle fibre membrane and appear to compress the fibres without causing necrosis. These fibres, and also non-invaded fibre, express class I major histocompatibility complex (MHC) protein products, which are not expressed in normal muscle.

Pathogenesis

In PM, it is presumed that cytotoxic T-lymphocytes recognize an antigen, bound to class I MHC products, on the muscle fibre surface. Muscle fibre function is compromised by the invading lymphocytes, which are also associated with lymphokine release. The nature and origin of the antigen are unknown.

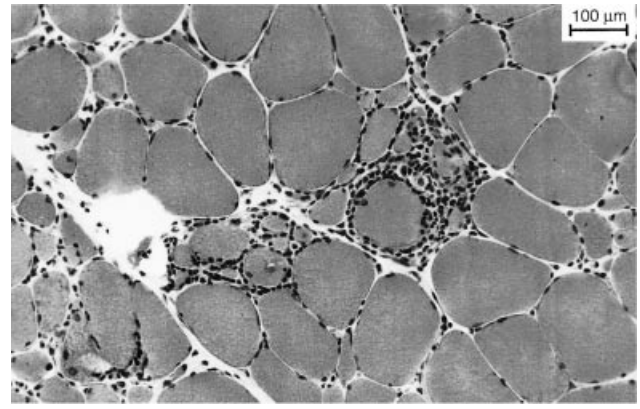

Figure 67.3 Polymyositis. Muscle biopsy (H&E, ×115). Note the endomysial inflammatory infiltrate.

Treatment

Despite the different pathogenetic mechanisms postulated, the immunosuppressive drug management of PM is the same as described above for DM. If there is extensive weakness and wasting at presentation, the prognosis for significant improvement is poor, although disease progress may be arrested.

Inclusion body myositis (IBM)

Clinical features

IBM is rare before the fifth or sixth decade of life and shows a strong male predominance.[11] Its incidence is uncertain and many cases have previously been labelled as (steroid-resistant) PM. Rare familial cases have been described.[12]

The characteristic pattern of muscle involvement, which is often asymmetric, involves wasting and weakness of quadriceps and distal weakness affecting finger flexion and ankle dorsiflexion. Symptomatic presentation is with falls due to the knees giving way and weakness of grip.

Dysphagia is relatively common and may be the presenting symptom.[13] Systemic features are not present. IBM has been reported in association with many other disorders, some autoimmune, but no consistent association has been recognized.[14]

Diagnosis and pathological features

The serum CK is normal or moderately elevated. EMG shows changes similar to those described for DM and PM but, in addition, 'neuropathic' features (long-duration, high-amplitude motor unit potentials) are often present. Whether this truly reflects neurogenic involvement or is a secondary consequence of primary muscle disease remains much debated.

The diagnosis has conventionally been established by light and electron microscopy.[15] Characteristic features (Figure 67.4) include the variable presence of inflammatory infiltrates (with a predominance of cytotoxic T-lymphocytes), partial invasion of muscle fibres, rimmed vacuoles, intracellular amyloid deposits and, diagnostically, 15–18 nm tubulofilaments (Figure 67.5).

There are arguments in favour of reviewing the conventional diagnostic criteria.[16]

Pathogenesis

Pathogenesis remains hotly debated. Although there is evidence of T-cell mediated cytotoxicity, it is not clear that this is of primary importance. The presence of myonuclear abnormalities suggests that IBM may be due to a disorder primarily affecting the cell nuclei. Protein aggregates in the characteristic inclusions contain amyloid and other proteins typical of the inclusions seen in the brain in Alzheimer's disease. Despite the pathological similarities, there is no clinical link between the two disorders, but it has been postulated that there may be similar protein degradation abnormalities in each disorder.[16,17]

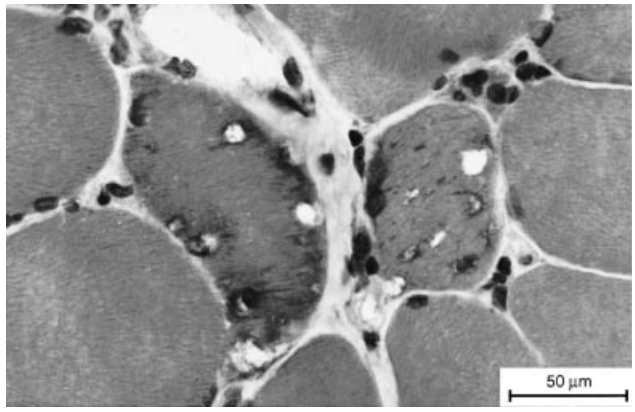

Figure 67.4 Inclusion body myositis. Muscle biopsy (H&E, ×460). Note the two fibres containing characteristic rimmed vacuoles.

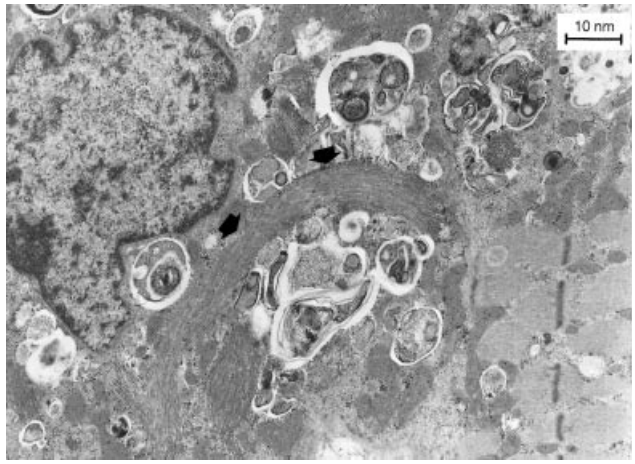

Figure 67.5 Inclusion body myositis. Muscle biopsy (electron micrograph, ×13 000). Bundle of characteristic 15 nm tubulofilaments (arrows).

Treatment

IBM appears to show little or no response to immunosuppressive therapies of the type that are successful in DM and PM and many specialists no longer recommend using such drug regimes. Early suggestions that intravenous immunoglobulin might be helpful have not been substantiated.[18]

The disease shows a relentlessly progressive course with loss of ambulation 10–20 years after onset.

Toxic and drug-induced myopathies

Toxic and drug-induced myopathies are an important, and almost certainly underdiagnosed, group of disorders, not least because prompt removal of the offending agent may lead to full recovery. Ethanol can cause a dramatic acute myopathy. It is much debated whether proximal weakness in chronic alcoholics is primarily myopathic or neurogenic in origin. Myopathy may be seen in association with drug abuse but of much greater significance are the myopathies associated with the therapeutic use of drugs.

Ethanol-related myopathies

Three forms of myopathy have been attributed to alcoholism. First, chronic alcoholics can develop painless proximal weakness, affecting the pelvic girdle more than the shoulder girdle. Serum CK may be modestly elevated. Muscle biopsy shows type II fibre atrophy.[19] Second, acute alcoholic myopathy follows a binge. There is muscle pain, swelling and weakness, which may be localized to one or two muscles or be generalized. The serum CK is markedly elevated. Myoglobinuria is present and may threaten renal function. Recovery of muscle function occurs over 1–2 weeks. Muscle biopsy shows muscle fibre necrosis and inflammatory infiltrates. Third, acute or subacute severe, painless, proximal weakness may be caused by hypokalaemia. Potassium loss may be secondary to diarrhoea or vomiting. Repletion of potassium leads to recovery.

Drug-induced

With the exception of drugs that cause hypokalaemia, the pathogenetic basis of most drug-induced myopathies remains unclear.[20] In practice, the most useful classification is based on the clinical features of the myopathy (Table 67.4). Statins have been associated with several forms of myopathy. Although the incidence is low, their widespread and ever-growing use means that most clinicians will encounter

Table 67.4 Patterns of drug-induced myopathy.

Painless
Painful
Acute rhabdomyolysis
Periodic weakness
Focal

statin-induced myopathy at some stage and therefore it merits separate discussion.

Painless myopathies

Painless myopathy is the most prevalent form of drug-induced myopathy, with corticosteroids being the commonest cause (Table 67.5). The clinical picture is of proximal weakness with either subacute onset or, more usually, chronic progression. Muscle atrophy develops in long-standing cases. Those drugs that produce hypokalaemia may also cause intermittent (periodic) weakness.

The clinical features of corticosteroid myopathy and Cushing syndrome are similar. Women are more susceptible to steroid myopathy than men and 9-α-fluorinated steroids (e.g. dexamethasone, betamethasone) have the greatest myopathic potential. The serum CK is usually normal. EMG may be normal or show 'myopathic' features. Muscle biopsy shows non-specific type II fibre atrophy (Figure 67.6). Full recovery usually follows drug withdrawal.

Painful

Many drugs may cause an acute or subacute painful myopathy and the list in Table 67.6 is certainly incomplete. Weakness is usually proximal but may be generalized and the muscles may be tender. The serum CK is often elevated and EMG shows changes of primary muscle disease. In some, there may be a direct toxic effect of the drug on muscle. In others, indicated in Table 67.6, there is an inflammatory myopathy.

Table 67.5 Drugs causing painless myopathy.

Amiodarone
Amphotericin[a]
Carbenoxolone[a]
Chloroquine
Colchicine
Corticosteroids
Diuretics[a]
Heroin
Liquorice[a]
Perhexiline
Purgatives[a]

[a]Drugs that cause hypokalaemia.

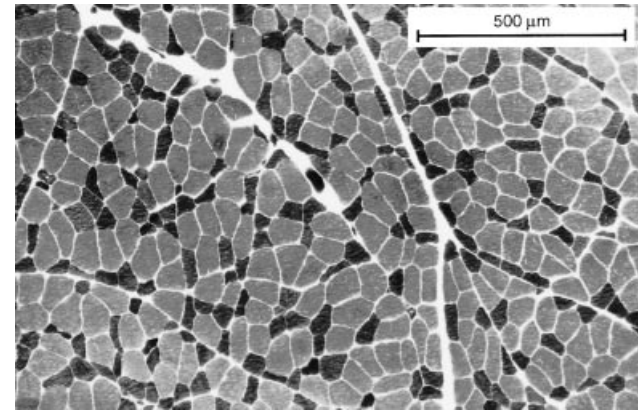

Figure 67.6 Type II fibre atrophy. Muscle biopsy (ATPase, pH 9.4, ×30). The type II fibres stain darkly.

Table 67.6 Drugs causing painful myopathy.

Amiodarone
Cimetidine[a]
Clofibrate
Ciclosporin
Danazol
D-Penicillamine[a]
Emetine
Gemfribrozil
Gold
Labetalol
Lithium
L-Tryptophan[a]
Nifedipine
Procainamide[a]
Salbutamol
Statins
Vincristine
Zidovudine

[a]Drugs causing an inflammatory myopathy.

Acute rhabdomyolysis

Acute rhabdomyolysis represents an extreme form of necrotizing myopathy with myoglobinuria and the clinical presentation is acute with severe generalized weakness and muscle pain. Muscle swelling may require fasciotomy and renal failure is common. Serum CK is very high. Drugs that cause this syndrome (Table 67.7) include drugs of abuse and addiction and drugs already noted to cause either painless or painful myopathy.

Periodic weakness

Drug-induced hypokalaemia (Table 67.5) may cause persistent or intermittent (periodic) weakness. Areflexia may be present during bouts of weakness. Serum CK may be elevated.

Table 67.7 Drugs causing acute rhabdomyolysis.

Amphetamine
Amphotericin B
Barbiturates
Carbenoxolone
Clofibrate
Cocaine
Diazepam
Gemfibrozil
Heroin
Isoniazid
Labetalol
Meprobamate
Methadone
Phenformin
Statins

Focal

Intramuscular injection of many drugs may cause local tissue damage. Repeated injections, particularly of certain antibiotics, pentazocine and opiates, may lead to muscle fibrosis and contractures.

Statin-induced myopathies

Statins (HMG-CoA reductase inhibitors) interfere with cholesterol synthesis and thus lower serum cholesterol levels. Already widely prescribed, some countries now allow these drugs to be sold over the counter without a prescription. There is no doubt that statins can cause myopathy, but despite numerous trials involving hundreds of thousands of patients, post-marketing surveillance and a publication rate of about one paper per week, for more than a decade, relating to statins and muscles, there remain many unanswered questions, including:

- What is the frequency of statin-induced myopathy?
- What is/are the underlying mechanism(s)?
- Are some statins more myopathic than others?
- Does the presence of a pre-existing muscle disease increase the risk of statin-induced myopathy?
- What other factors lead to increased risk of statin-induced myopathy?

Many reviews have appeared, mostly in the cardiology and lipid literature, and terms such as myositis and rhabdomyolysis have often been used inappropriately, causing some confusion.[21] Extraordinarily, many reports have relied solely on patient self-reporting without physician assessment and very few have included formal assessment of muscle function – not even the simplest bedside assessment of muscle strength. As to possible mechanisms, strong suspicion falls upon disturbance of intermediary metabolism although by and large this remains unproven. Statins block pathways associated with lipid synthesis and might therefore be expected to have some impact on muscle fibre membrane composition; membrane fragility underlies many other forms of myopathy, including many of the dystrophies. In addition, they block pathways involved with coenzyme Q (CoQ10) synthesis, an essential component of the mitochondrial respiratory enzyme pathway. This has led some enthusiasts to recommend prescribing CoQ10 with statins, but the theoretical mechanism has not been proven, nor the therapeutic approach shown to work.

Although the earlier literature referred to statin-induced myositis, there had in fact been only a handful of reports showing true myositis (i.e. inflammatory infiltrates in muscle) – rather, those inexperienced in the field of muscle disease used the term myositis to describe anyone with a substantially elevated serum CK level. More recently, there have been reports of myositis developing in patients on statins and persisting after the statin was withdrawn, to the extent of requiring immunosuppressant drug therapy.[22] But uncertainties remain. These patients had not had their CK measured before starting treatment and so possibly the myositis predated the introduction of the statin. The development of myositis might have been entirely coincidental – after all, with statins being so widely prescribed (approximately 1 in 20 of the UK population at present and growing), such coincidence is bound to occur. Also, in five of the eight reported cases, the pathological appearance was of a necrotizing myopathy, without inflammatory infiltrates, although MHC 1 expression, often regarded as a surrogate for an inflammatory process, was increased. Further assessment, by suitably experienced myologists, is required.

On the basis of currently available (but flawed) evidence, it would appear that the major statin-induced muscle syndromes include:

- asymptomatic elevation of serum CK;
- myalgia with elevated serum CK (probably the commonest);
- myalgia with normal serum CK;
- acute rhabdomyolysis with risk to renal function;
- a true myositis which may persist after discontinuation of the statin;

The most feared complication is acute rhabdomyolysis with the attendant complication of renal failure secondary to myoglobinuria. One of the earlier statins, cerivastatin, was withdrawn following a number of deaths attributed to this. Overall, the risk of rhabdomyolysis is extremely low but certain factors predispose to it, most notably the dose of the statin and the concomitant use of other drugs that interfere with statin metabolism.

A recent announcement from the US Food and Drug Administration (FDA) concluded that with respect to simvastatin, the risk of rhabdomyolysis was substantially increased at a dose of 80 mg daily compared with lower doses.[23] The risk is substantially increased when combined

with certain other drugs and they advised on the maximum dose of simvastatin to be used in combination with those drugs. Thus, if also taking diltiazem, simvastatin should be limited to 40 mg daily, if taking amiodarone or verapamil to 20 mg daily and if taking gemfibrozil or ciclosporin to 10 mg daily. A number of drugs should never be combined with simvastatin.

Although it has been suggested that a pre-existing myopathy increases the risk of statin-induced myopathy, the evidence is not convincing and it should certainly not be considered an absolute contraindication to their prescription. Patients should be counselled at the time of prescription about the potential myopathic effects and to report symptoms such as myalgia, weakness or myoglobinuria.

There have been many reports of patients who have been identified as having a myopathy (e.g. McArdle disease) following investigation of an elevated serum CK, which was measured only because the patient was on a statin! Another important catch is the patient with subclinical hypothyroidism causing myalgia, hypercholesterolaemia and an elevated serum CK. Interpretation of symptoms such as myalgia is difficult when patients have been forewarned of its possibility.

There remains debate as to whether CK should always be measured before starting statins, so as to have a baseline if there are future problems. An argument against this is cost, especially as the majority of patients will not develop muscle problems. Another difficulty is the lack of a clear-cut upper limit of normal for CK and that CK levels may be increased following normal patterns of physical activity – many normal individuals will be reported by the laboratory as having an elevated CK which may then cause anxiety and unnecessary investigation.

Finally, there have been reports of myasthenia gravis developing after starting a statin or pre-existing myasthenia worsening after starting such treatment. As discussed above with respect to other myopathies, it remains uncertain whether these are real problems or biased reporting of coincidence. However, it seems reasonable to caution patients accordingly.

Endocrine and metabolic myopathies

Myopathy, typically in the form of chronic painless proximal weakness, is common in endocrine disorders and of particular importance because treatment of the underlying disorder almost invariably leads to full recovery.[1] In the elderly, the most frequently encountered endocrine myopathies are those associated with thyroid disease, glucocorticoid excess (Cushing syndrome and iatrogenic steroid myopathy) and disorders of vitamin D metabolism.

Thyroid disorders

Hypothyroidism (see Chapter 98, thyroid disorders)

Symptomatic myopathy is present in about 80% of patients with hypothyroidism but is rarely the presenting feature. Symptoms include weakness (mild and proximal), fatigue, stiffness and myalgia. Examination may show delayed tendon reflexes and myoedema – a ridge or mound of contracted muscle seen transiently after pinching or percussing muscle.

The serum CK is elevated, often markedly, in most patients and thyroid function studies should be performed in any patient with unexplained elevation of the CK.

Thyroid function studies are invariably abnormal and the myopathy resolves on restoration of the euthyroid state.

Hyperthyroidism (see Chapter 98, thyroid disorders)

Up to half of thyrotoxic patients will have weakness as a symptom and over 80% of patients have signs of weakness at presentation. Onset of myopathy is usually subacute or chronic and the weakness, which is proximal, is generally greater than that seen in hypothyroid myopathy. However, in thyrotoxic myopathy the serum CK is often normal. The weakness resolves upon resolution of the thyrotoxicosis.

Graves' ophthalmopathy

Thyroid-associated eye disease, although most frequently associated with hyperthyroidism, can occur in euthyroid and hypothyroid patients.[24] Diplopia may be the only feature but the typical order of progression of eye symptoms and signs is eyelid lag and retraction, itchiness, redness of the conjunctivae, eyelid swelling, proptosis, diplopia, corneal ulceration, papilloedema and optic nerve compression. These changes may be unilateral.

Biochemical evidence of thyroid dysfunction is usually readily evident but if thyroid-associated eye disease is suspected and serum thyroid hormone and thyroid-stimulating hormone levels are normal, then immunological studies may be helpful.[25] Orbital ultrasonography, CT and MRI show characteristic extraocular muscle swelling which may aid diagnosis if laboratory support for the diagnosis is lacking.

The first stage of treatment is to return thyroid function to normal. If major eye signs persist, options include surgical decompression of the orbit, steroids and orbital irradiation.[26]

Pituitary–adrenal axis disorders (see Chapter 97, the pituitary gland)

The clinical features of Cushing syndrome (whether pituitary, adrenal or ectopic) and iatrogenic steroid myopathy (see the earlier sections) are similar.[1] Weakness starts around the pelvic girdle and later ascends to the trunk

and then the shoulder girdle musculature. Myalgia is common. It is rare for myopathy to develop without other features of glucocorticoid excess.

The serum CK is usually normal, EMG shows myopathic features and muscle biopsy shows type II fibre atrophy (Figure 67.6). The myopathy resolves once the glucocorticoid excess is removed.

Rarely, an acute myopathy [acute quadriplegic myopathy (AQM)] may develop following high-dose parenteral steroid therapy, with or without concomitant use of neuromuscular blocking agents, for example, for the treatment of myasthenia gravis or status asthmaticus.[27] Pathologically, it is characterized by loss of thick (myosin) filaments.[28]

Disorders of vitamin D metabolism

The myopathic disorders associated with osteomalacia and with primary hyperparathyroidism show clinical similarities.[1]

Osteomalacia

Pelvic girdle weakness, causing a waddling gait and difficulty climbing stairs and getting out of low chairs, is the presenting symptom in about one-third of patients with osteomalacia.[29] It is almost invariably associated with bone pain, most prominent in the ribs, pelvis and femora.

The serum CK is usually normal, as is muscle biopsy, although non-specific changes may be seen.

With appropriate treatment the weakness slowly improves, but the bone pain usually resolves more rapidly.

Primary hyperparathyroidism (see Chapter 95, endocrinology of ageing)

Weakness and fatigue may be late features of primary hyperparathyroidism but it is not clear whether this is neurogenic or myopathic in origin.[1] Successful treatment (usually involving removal of a solitary parathyroid adenoma) leads to resolution of the neuromuscular symptoms.

Paraneoplastic myopathies

Up to 20% of patients with DM, but probably significantly more in the elderly, have an associated malignancy (see earlier sections), but the pathogenetic mechanism is unclear. Serum electrolyte disturbances (hypokalaemia, hyperkalaemia, hyponatraemia and hypercalcaemia) caused by neoplastic disorders, including tumours of endocrine glands, are one cause of paraneoplastic muscle weakness. Benign or malignant tumours of endocrine glands may also cause weakness through hormone deficiency or excess.[30]

The term carcinomatous neuromyopathy is sometimes used to describe a syndrome of proximal weakness and wasting (usually pelvic more than shoulder girdle), of subacute or chronic course and with depressed tendon reflexes. Most evidence suggests that this is probably neurogenic rather than myogenic in origin.

Inherited myopathies

Muscular dystrophies

The term muscular dystrophy encompasses a group of progressive, inherited disorders in which the primary pathological process is degeneration of muscle fibres. Although clinically highly variable, common histological features include muscle fibre necrosis, abnormal variation in fibre size, central nucleation, fibre splitting and replacement of muscle by fibrous tissue.

The classification of the muscular dystrophies is in a state of change as the genetic and molecular basis of each disorder is identified. In everyday clinical practice, the most useful classification is based upon the mode of inheritance and phenotype (Table 67.8). Myotonic dystrophy is considered separately (see the following sections). Most muscular dystrophies present in childhood or early adult life, but there are important exceptions (including myotonic dystrophy). Some may first present in middle and late middle age, whereas others may be asymptomatic and be identified serendipitously when a relative is assessed following identification of another affected family member.

Dystrophinopathies

Duchenne and Becker muscular dystrophy are allelic disorders. A mutation causing complete absence of the protein dystrophin causes the severe Duchenne phenotype, but mutations resulting in the production of some functional dystrophin cause Becker muscular dystrophy, which itself has a variable clinical presentation.

In Duchenne muscular dystrophy, onset occurs between 2 and 4 years of age and death occurs in early adult life. In typical Becker muscular dystrophy, onset is during adolescence. Rarely, first presentation, with pelvic weakness, may occur in late middle age.[31] Cardiomyopathy is common and may be severe even in the absence

Table 67.8 Classification of the muscular dystrophies.

X-linked inheritance
• Duchenne
• Becker
• Emery–Dreifuss
Autosomal dominant inheritance
• Facioscapulohumeral
• Oculopharyngeal
• Limb-girdle
• Emery–Dreifuss
Autosomal recessive inheritance
• Limb-girdle

of significant skeletal muscle weakness.[32] About 10% of female Duchenne/Becker dystrophy carriers may manifest myopathic features, ranging from asymptomatic calf hypertrophy to severe limb-girdle weakness, the latter sometimes not presenting until middle age.

Limb-girdle dystrophies

About 90% are autosomal recessive and 10% autosomal dominant. The common phenotype is progressive limb-girdle weakness, usually affecting the pelvic girdle more than the shoulder girdle, but with a very wide range of age of onset and severity. In the majority, presentation is in childhood or early adult life. A few are associated with cardiomyopathy. None typically present beyond middle age. Diagnosis depends upon immunohistochemical techniques applied to muscle biopsy and DNA analysis.

Facioscapulohumeral (FSH) muscular dystrophy

FSH muscular dystrophy is relatively common (prevalence about 4 per 100 000 population). It is an autosomal dominant disorder associated with deletion of a repeat sequence, not within a gene, on chromosome 4.

The name describes the highly characteristic pattern of early muscle involvement. The patient may not be aware of facial weakness and it may be missed by an inexperienced clinician. The patient may report an inability to whistle, use a straw or blow up balloons. Weakness and wasting of the scapular fixator muscles (Figures 67.7 and 67.8) limits upper limb abduction and patients complain of difficulty combing their hair and reaching up to shelves. There is weakness and wasting of the humeral muscles (biceps more than triceps) but preservation of deltoid. Unlike other forms of muscular dystrophy, the weakness is often asymmetric (Figure 67.9). Tibialis anterior is involved early and weakness is nearly always found on examination. The patient may have symptomatic foot drop.

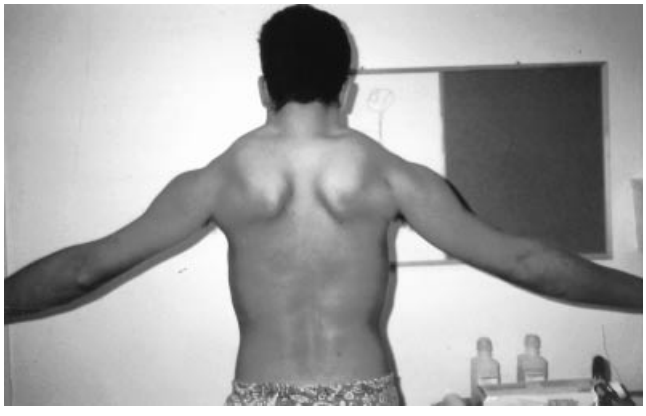

Figure 67.7 Facioscapulohumeral muscular dystrophy (see text).

Figure 67.8 Facioscapulohumeral muscular dystrophy (see text).

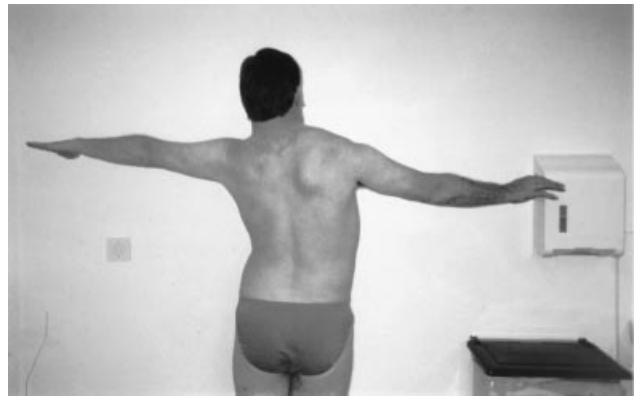

Figure 67.9 Facioscapulohumeral muscular dystrophy (see text).

The age of onset is highly variable but is typically in adolescence and early adult life. Mildly affected cases are common and family studies frequently identify asymptomatic individuals with mild weakness. There is slow progression of the weakness, with later involvement of the pelvic girdle. The serum CK may be normal or modestly elevated. Diagnosis is by DNA analysis.

Oculopharyngeal muscular dystrophy

This is an autosomal dominant, late-onset disorder which is probably underdiagnosed.[33] Onset is usually in the fifth decade or later and most frequently with ptosis (Figure 67.10), which can be asymmetric. There is overactivity of frontalis in an attempt to compensate for the ptosis (Figure 67.10). Dysphagia develops within a few years and is occasionally the presenting symptom.

In later stages, eye movements may be restricted (external ophthalmoplegia) but diplopia is rare. Limb involvement is usually confined to mild shoulder girdle weakness, but the pelvic girdle can be involved and rarely there is more debilitating limb weakness.

Figure 67.10 Oculopharyngeal muscular dystrophy (see text).

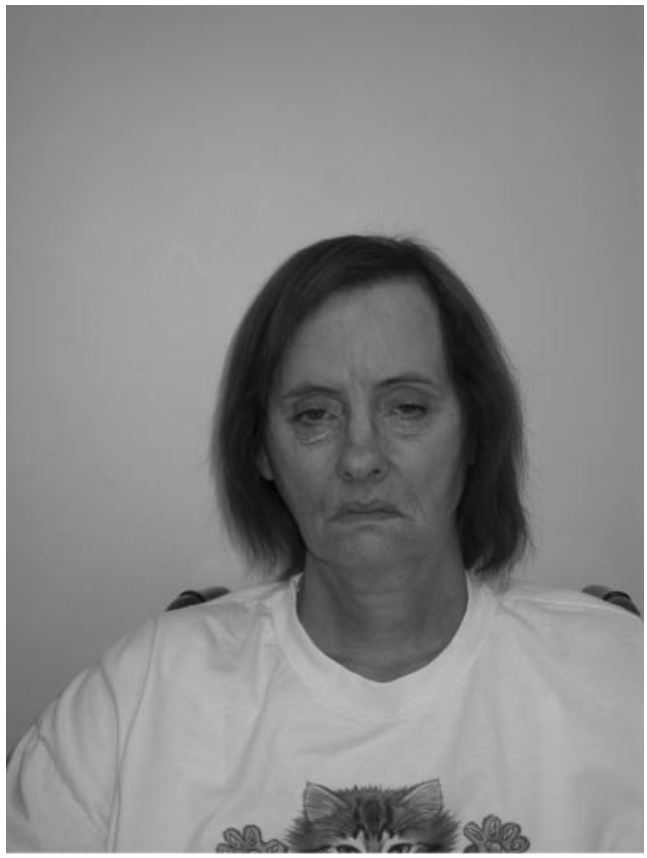

Figure 67.11 Myotonic dystrophy. Characteristic facial appearance. Note the ptosis and wasting of the facial muscles and temporalis.

Ptosis can be severe enough to impair vision – surgical correction can be highly successful. Dysphagia may respond to oesophageal dilatation or cricopharyngeal myotomy but requires detailed preoperative assessment.

Diagnosis is by DNA analysis, demonstrating an expansion in the PABPN1 gene. The differential diagnosis of late-onset ptosis and dysphagia includes myasthenia gravis and mitochondrial chronic progressive external ophthalmoplegia (CPEO) (see the following sections).

Myotonic dystrophy

Two forms of myotonic dystrophy (DM) are now recognized, sharing a common molecular mechanism. They are autosomal dominant multisystem disorders. In each, an unstable nucleotide repeat expansion probably has its effect through disruption of mRNA metabolism.[34,35] Diagnosis is by DNA analysis.

DM1 is the commonest form of muscular dystrophy in adult life.[36] The disease shows anticipation, by which subsequent generations tend to show a more severe expression of the disease, as a result of the instability of the underlying repeat expansion.

Clinical features of the 'classical' form include onset from late childhood to middle age, ptosis, weakness that involves initially facial muscles (Figure 67.11), sternomastoid and distal upper limb muscles but later spreads to proximal muscles, respiratory muscle involvement, frontal balding, cataracts, cardiac conduction defects, gonadal atrophy and impaired fertility, excessive daytime sleepiness and impaired smooth muscle function. Myotonia is most evident in the hands and patients complain of difficulty in relaxing their grip. Overall, IQ scores are lower than average. A severe congenital form is seen in a proportion of children born to mothers who themselves have the later-onset form.

In family studies, it is common to identify family members in late middle age who are unaware that they have the disorder. They may be asymptomatic, but frequently have had cataracts that were not recognized as being due to myotonic dystrophy. Even though oligosymptomatic, it is important to identify such patients because they are still at risk of developing cardiac conduction defects and respiratory insufficiency (with particular risk of both during and after anaesthesia).

Major management issues include the identification and appropriate treatment of cardiorespiratory problems and identification of asymptomatic family members who carry

the gene and are at risk of themselves developing cardiorespiratory problems or, for women, of having a congenitally affected child.[37]

DM2 shows many similarities, but tends to be a relatively milder disease presenting later in life, and the weakness is more proximal than distal.[38] Muscle pain is a common presentation.

Chronic progressive external ophthalmoplegia (CPEO)

Progressive ptosis and limitation of eye movements, with or without diplopia, may be seen in a number of disorders (Table 67.9). Myasthenia gravis must always be considered and diagnosis can be difficult if the disease is limited to the ocular muscles. In oculopharyngeal muscular dystrophy, ptosis is an early feature but limitation of eye movements occurs late and is rarely severe.

Most patients with mitochondrial CPEO have an abnormal muscle biopsy showing ragged red fibres (Figure 67.12). Mitochondrial DNA studies typically show a deletion. In the elderly, most cases are sporadic, but autosomal forms exist.[39]

Acknowledgements

I am grateful to Dr Waney Squier for providing the histological illustrations and to my patients for allowing their photographs to appear.

Table 67.9 Differential diagnosis of chronic progressive external ophthalmoplegia.

Myasthenia gravis
Oculopharyngeal muscular dystrophy
Mitochondrial cytopathy
Thyroid eye disease

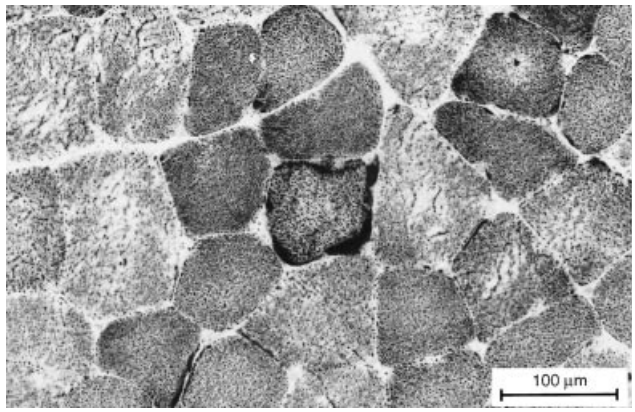

Figure 67.12 Mitochondrial cytopathy. Muscle biopsy (modified Gomori trichrome, ×230). Note the single ragged fibre.

Key points

- Drug-induced myopathies are common and underdiagnosed.
- Statins are likely to become the commonest cause of drug-induced myopathy.
- A few inherited myopathies may not present until late middle age.
- The history and examination are generally more powerful tools than laboratory investigation.
- Inclusion body myositis is the commonest acquired myopathy in the elderly.

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CHAPTER 68

Motor neurone disease

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Introduction

The first clear account of motor neurone disease (MND) emerged in the mid-nineteenth century,[1] although this consolidated earlier observations such as by Aran.[2] However, MND care remained fragmented well into the 1980s,[3] and it is only in the last 25 years that the disease has received much public and professional attention. In part, the increased profile of MND is due to a few public figures who were diagnosed with the disease, for instance, the actor David Niven and the sportsman Lou Gehrig. The role of patient support organizations in many different countries must also be acknowledged for fighting their corner to obtain more resources for treatment and research. Much of the current medical and legal interest in euthanasia and physician-assisted suicide has centred on MND and similar disorders. The preservation of mental capacity in the majority of patients with this condition and the relatively predictable pace of decline have made MND an ideal candidate disease for focusing debate on end-of-life issues. Developments in medications, both disease-modifying[4] and those involved in symptom control, assistive technology and innovative healthcare delivery systems have given hope and relief to patients with MND and to their caregivers. Multidisciplinary teams are now widely involved in MND care and there is a greater acceptance of involving palliative care services at an early stage.

Definition and terminology

The term motor neurone disease either can be used to describe the condition known as *amyotrophic lateral sclerosis* (ALS) or it can be a more general term for other motor neurone diseases including bulbar palsy and progressive muscular atrophy (PMA) which are closely allied to ALS and others such as Kennedy disease and Hirayama disease that have a less clear association. Conditions such as progressive bulbar palsy and PMA can develop into ALS although pure forms of these conditions also occur. The relationship of ALS to subtypes such as the 'man in a barrel' or flail arm MND (Vulpian–Bernhardt syndrome) and flail leg MND (pseudopolyneuritic MND) is not clear. PMA can either be a very slowly progressive disorder with an outlook better than for ALS or it can progress rapidly, sometimes over a few months, giving it a bimodal distribution of survival. Over half of all cases of PMA show the corticospinal tracts to be involved at autopsy and ubiquitin inclusions typical of MND are also found in the central nervous system (CNS).[5] Bulbar symptoms and signs are seen in a minority of patients with PMA. This chapter deals largely with the ALS form of MND. Bulbar palsy remains a useful term referring to dysarthria and/or dysphagia being the presenting symptoms, but in most cases the condition eventually progresses to MND. The usefulness of the term bulbar palsy is a prognostic one – the life expectancy in bulbar palsy is significantly worse than that in limb-onset MND. A subcommittee of the World Federation of Neurology made a significant contribution to the definition of MND and ALS when it met in El Escorial, Spain, to formulate a set of internationally agreed diagnostic criteria.[6] The El Escorial criteria for diagnosis of possible, probable and clinically definite MND have made it possible to compare directly the results of research investigations carried out in different countries. The criteria are summarized below:

- *Definite ALS:* Upper and lower motor neurone signs in bulbar and two spinal regions or in three spinal regions (cervical, thoracic and lumbosacral).
- *Probable ALS:* Upper and lower motor neurone signs in at least two regions with some of the upper motor neurone signs rostral to the lower motor neurone signs.
- *Probable ALS/laboratory supported:* Upper motor neurone signs in at least one region and lower motor neurone signs on electrodiagnostic testing in at least two regions.
- *Possible ALS:* Upper and lower motor neurone signs in one region (the same region) or upper motor neurone signs in two or three regions or upper and lower motor neurone signs in two regions with no upper motor neurone signs rostral to the lower motor neurone signs.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

The term 'suspected ALS' was dropped in the 1998 revised criteria. It previously referred to a condition in which lower motor neurone signs were found in two or three regions. Certain clinical features were listed as deflecting one from the diagnosis (although not absolute exclusions). These included sensory dysfunction, sphincter disturbance, autonomic signs, visual abnormalities, involuntary movement disorder and cognitive dysfunction. The criteria require the exclusion of other diagnoses by imaging and other investigations. The Airlie revision[6] also suggested that neurophysiological or pathological criteria could be used to identify lower motor neurone signs. The Awaji consensus[7] clarified the neurophysiological features of acute denervation in MND. These criteria are widely supported and adoption of these revisions may drop the 'probable ALS/laboratory supported' entity. There remains a group of patients who do not satisfy these criteria but who are thought to have MND on clinical grounds. These are mainly lower motor neurone syndromes. They emphasize the point that the El Escorial criteria with their several revisions remain important research tools but do not replace clinical judgment.

Clinical features

MND is a progressive neurodegenerative disorder of the upper and lower motor neurones, resulting in weakness, muscle wasting, fasciculation and spasticity as a part of the clinical picture. There is a profound difference between the motor pathways, which are severely affected, and the sensory pathways, which are relatively preserved. Sensory pathway involvement is sufficiently unusual as to spark off a search for an alternative diagnosis. About one-third of patients with MND present with bulbar symptoms, the others with limb problems. Older patients and women are more likely to present with bulbar symptoms. Only a few have other initial presentations such as dementia or respiratory failure. These groups follow significantly different clinical courses and the distinction between them remains important. Furthermore, the diagnostic pitfalls in the two main modes of presentation may be completely different (see below). MND is slightly more common in men, although recent information suggests a narrowing of the male:female ratio. The mean age at presentation is about 57 years. This is a few years younger than the mean age for other neurodegenerative disorders of adult life, such as Parkinson's disease (PD) and Alzheimer's disease. A few patients with MND develop parkinsonism as well and a further few develop dementia. The dementia of MND is a frontotemporal one and distinct from Alzheimer's disease. It is characterized by behaviour disturbance, impaired judgment, language and memory problems and a dysexecutive state.[8] Only small numbers of patients develop these features but they do underline the point that common mechanisms of disease aetiology may be involved in these seemingly disparate disorders. In an even smaller number of cases, patients can present with simultaneous development of both ALS- and PD-like features.

Limb-onset MND

This can arise in either arms or legs and common modes of presentation are with weakness, wasting, cramp, spasms secondary to spasticity and fasciculation. The symptoms are progressive usually over a period of months or occasionally over a few years. Loss of manual dexterity secondary to involvement of small hand muscles is a frequent presenting symptom, as is a disturbance in gait and, in older patients, falls. A cramp in muscles not normally thought of as being prone to cramp, for instance, forearm flexors or abductor pollicis brevis can be a useful clinical pointer. A history of progression is an essential requirement for the diagnosis. The disease commonly starts in just one limb. Clinical and prognostic separation of different limb-onset varieties of MND is still poorly developed, but distinct entities such as flail arms MND, hemiplegic MND and paraplegic MND are recognized. Pain, which is not uncommon in late disease, is usually not a problem at presentation and its early occurrence should encourage a search for alternative diagnoses. Although fasciculation is seen very commonly in MND, it is unusual for prominent fasciculation to be the sole presenting symptom in MND, but it is a common symptom in patients with benign fasciculation or those with a fear of developing MND. Patients with a family history of MND are exceptions, in that they frequently have fasciculation as a presenting symptom.

Bulbar-onset MND

This occurs in about one-third of patients with MND and is more frequent in women. The first presentation is usually with dysarthria or anarthria. Older patients are also more likely to have bulbar onset disease. Progression from dysarthria to anarthria can, in some cases, be so rapid as to lead to an erroneous diagnosis of stroke. Dysphagia is also common in the disease but is a surprisingly infrequent presenting symptom. Recurrent aspiration pneumonitis should alert the physician to the possibility of MND. Choking spells are also uncommon at presentation. Dyspnea secondary to respiratory muscle weakness with or without aspiration pneumonitis is another rare mode of presentation but can become a more troublesome problem later in the disease, as discussed below. Emotional lability is often encountered but only rarely at first presentation and then not as troublesome as other bulbar symptoms.

In establishing a diagnosis of MND, the absence of certain symptoms is just as helpful as the presence of others. Sensory symptoms are usually absent at first presentation

of MND and, when present, they are usually trivial in comparison with the motor problems. The presence of sensory symptoms in a patient at first presentation should activate a search for a condition other than MND. Clinically relevant sensory signs are even less common, and when they are found are often attributed to, but cannot always be explained by, the consequences of nutritional deprivation or pressure palsies secondary to profound wasting and weakness. Sophisticated electrophysiological measurements can demonstrate involvement of sensory pathways in up to 50% of patients. Urinary bladder function is generally preserved in MND. Urgency and frequency, encountered so commonly in other patients with limb spasticity, are uncommon in MND. Similarly, the anterior horn cells responsible for eye movements are relatively resistant to the diffuse process that damages other anterior horn cells in MND, with abnormalities being found occasionally in patients on long-term ventilatory support.

Familial MND

Up to 10% of MND is familial and largely inherited in an autosomal dominant pattern. The age of onset and the clinical course of this condition are similar to those of the sporadic disease, indicating that common mechanisms may be involved in disease causation. Missense and nonsense mutations in the gene encoding superoxide dismutase type 1 (SOD 1 or ALS 1) are found in about 10% of families with this disease.[9] Some mutations (e.g. A4V) encode for more rapidly progressive disease than others (e.g. G37R).[10] SOD 1 MND more commonly starts in the legs. Other genes have also been identified as causing MND but none are as well studied as SOD 1. SOD 1 toxicity is increased in experimental animals by the close proximity between mutation-carrying astrocytes and anterior horn cells. ALS 2 is a recessive disorder involving a gene encoding GEF signalling. Interest in other genetic causes of motor neurone disorders has focused on angiogenin, TAR DNA binding protein (TARDBP), vascular endothelial growth factor (VEGF), dynactin, senataxin, vesicle-associated membrane protein-associated protein B (VAPB), microtubule-associated protein tau (MAPT) and unknown loci on chromosome 9 linking MND with frontotemporal dementia.[11] The ubiquitinated inclusions found in MND contain TDP43, the protein encoded by TARDBP. TARDBP mutations are found in 2–5% of patients with familial MND and in about 2% of sporadic MND cases.[12] It is also controversially suggested that RNA processing defects play a role in MND. The X-linked disorder Kennedy disease or spinal bulbar muscular atrophy (SBMA) is an MND-like disorder with a better outlook than MND and should be considered in cases where maternal transmission of MND is likely or when specific clinical features (see the section on differential diagnosis below) alert one to the diagnosis. There are various genetic factors that may alter disease expression in sporadic MND. For instance, homozygous survival motor neurone 2 (SMN2) gene mutations are over-represented in the MND population. Mutations in the gene encoding vascular endothelial growth factor (VEGF)[13] may also have a disease-modifying effect. Other potential genetic risk factors for MND include mutations in the apurinic/apyrimidinic endonuclease (APEX nuclease) gene, the neuronal apoptosis inhibitory polypeptide (NAIP) gene, cytochrome *c* oxidase gene and the APO E4 genotype. Young patients with an MND-like syndrome may have mutations in the hexosaminidase A gene, causing an accumulation in tissues of GM2 ganglioside. The principles of investigation and management of familial disease are the same as those of sporadic MND with the exception of issues of genetic counselling and perhaps additional psychological support for those patients who have previously nursed other family members through a distressing and ultimately fatal condition. Genetic counselling is made more difficult by the incomplete penetrance of the mutant gene. Where ethical considerations permit this, FALS may provide the best opportunity to study the effects of potentially neuroprotective strategies in altering the course of disease expression in presymptomatic individuals who are known to carry pathogenic disease mutations. The human SOD 1 mutant gene has made it possible to develop a very good mouse model of MND.[14] This allows screening of potential therapeutic compounds before they are used in clinical settings.

Clinical course

Both bulbar-onset and limb-onset MND progress inexorably and are ultimately fatal. The rate of progression is variable but the clinical course is more predictable than for many other fatal conditions such as some of the malignant diseases. This point is important in enabling the healthcare needs of patients to be anticipated and planned for. Median survival in MND is approximately 3 years from the first symptom. Survival up to 5 years and beyond is certainly seen and 10% are said to survive over 10 years. However, survival to 10 years or beyond should activate a search for alternative diagnoses as some of the mimic syndromes have slower progression. Despite the anecdotal observation of more patients surviving to previously exceptional durations of disease, systematic studies do not show an overall increase in survival in MND. Although some patients appear to go through periods of relative stability, these are the exception rather than the rule in MND (except in young-onset MND where initial severe deterioration can be followed by prolonged stability). Each 6 month period usually sees an increase in disability. Women are over-represented in the bulbar-onset group and have a worse prognosis than men. Other prognostic factors include short

latency between symptom onset and diagnosis (perhaps coding for more rapidly advancing disease), older age at presentation and poor social support network. MND patients with a spouse-carer live longer.[15]

Differential diagnosis and diagnostic pitfalls

MND does not have a diagnostic test or reliable biomarker and is a rapidly progressive condition. This makes it imperative to look for alternative diagnoses that may be more treatable or carry a better outlook. Diagnostic errors are more likely to occur if there is pressure for early diagnosis. This is happening now owing to advances in treatment and to increased publicity for the disease. Patients who have fasciculation either as a constant finding, or more often as an intermittent symptom, confined to one muscle or segment such as one calf worry about having MND. In the absence of other signs of a progressive disorder, these patients are likely to have benign fasciculation requiring explanation and reassurance but no other intervention. In an Irish study of diagnostic pitfalls, errors included patients regarded as having clinically definite or clinically probable MND who later turned out to have postpolio syndrome or Kennedy disease. The searches for a biomarker for MND may change diagnostic certainty in years to come.

Cervical and/or lumbar spondylosis

Spinal root and cord compression by cervical and lumbar spondylosis is common. Root compression can lead to segmental muscle wasting and weakness and is a common cause of calf muscle fasciculation. In the elderly, multiple root compression can cause fairly widespread lower motor neurone signs. This, combined with the spasticity that can be caused by spinal cord compression, can mimic MND. However, sensory and bladder disturbances are common in spondylosis but are spared in MND. Neck pain and restriction of neck movements are also more common in spondylosis than in MND at its onset. Bulbar signs, when present, clearly point more strongly towards MND. Tongue wasting with fasciculation can be diagnostic in this setting and other bulbar signs can be suggestive – for instance, brisk jaw jerk or jaw clonus, spastic dysarthria or emotional lability.

Other spinal pathology

Occasionally the distinction between MND and spinal conditions such as syringomyelia can be difficult (a few patients with syringomyelia present with motor rather than sensory features), but spinal MRI can distinguish between these conditions. Other intrinsic spinal pathology may also mimic MND but such cases are rare in the West. Cysticercosis of the spinal cord has been linked with an MND-like presentation and needs to be considered in endemic areas, particularly when the presentation is with a disturbance in one limb, so-called monomelic myelopathy or amyotrophy. Hirayama disease is a disorder of younger men causing distal and usually unilateral arm amyotrophy.[16] It can be familial and may involve dynamic spinal cord compression during neck flexion, resulting in damage to genetically predisposed anterior horn cells. Inherited disorders of spinal neurones can be mistaken for MND including its familial form. Hereditary spastic paraparesis can be a predominantly motor disorder of the upper motor neurones and lower motor neurone disturbance is not a feature, but spontaneous clonus can mimic fasciculation and the unwary can be caught out. The prolonged history and relatively indolent clinical course are also powerful indicators away from MND. The term *primary lateral sclerosis* was coined to describe those patients who have a slowly progressive upper motor neurone disturbance without lower motor neurone features over at least a 3 year period of observation. The progression of this condition is slower than that of MND and the prognosis better. Spinal muscular atrophies, previously classified as forms of MND, are now recognized as distinct disorders with a more benign course. Kennedy disease or X-linked bulbospinal neuronopathy is a disorder characterized by lower motor neurone disturbance of spinal and bulbar neurones and was previously frequently mislabelled MND. This should happen less frequently now as features such as gynaecomastia, facial fasciculation and a family history of X-linked disorder should lead to the search for the trinucleotide repeat expansion in the androgen receptor gene.[17] Other clues include finding low sensory action potentials on nerve conduction studies. Sandhoff disease, a variety of gangliosidosis with hexosaminidase A deficiency, can present in an MND-like fashion and needs to be considered as a possible diagnosis in any very young patient with apparent MND.

Inflammatory lower motor neurone disorders

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a radiculoneuropathy with predominantly motor symptoms and signs and without upper motor neurone pathology. It can mimic the lower motor neurone disturbance of MND but the finding of slowed nerve conduction velocities and elevated CSF protein should lead to the correct diagnosis of a neuropathy rather than an anterior horn cell disorder. This is a treatable disorder often responding well to immunomodulation such as with intravenous immunoglobulins (IVIG). A more patchy related disorder, multifocal motor neuropathy (MMN) with proximal conduction block, also causes confusion.

In MMN, the response to steroids and plasmapheresis is poor and the response to IVIG is rather better to begin with (in 70%) than in CIDP. However, it may not be as sustained. It, too, is worth thinking about in the patient with few or no upper motor neurone signs and without bulbar involvement, with asymmetric onset often in upper limbs and with weakness out of proportion to wasting being important clinical clues. Those cases refractory to IVIG may respond to cyclophosphamide. Reflexes can be preserved and, although it is a neuropathy, fasciculation can be prominent. Limited autopsy studies suggest that anterior horn cells may also be affected. Antibody binding to the nodes of Ranvier indicates that this may be the site of damage. There is a syndrome of late deterioration in patients who have had polio in childhood or in early adult life. This postpolio syndrome can resemble MND but follows a different clinical course. Its recognition is easy if the history of pre-existing polio is known. Similarities between the viral condition and idiopathic MND have prompted searches for an aetiological association between the two disorders. Other enteroviruses have also been implicated in the aetiology of MND. Vasculitis affecting either the spinal cord or the spinal roots or both can resemble MND. Unusually marked sensory symptoms or other features of systemic vasculitis can act as clues. CSF examination can be helpful in this situation as the CSF protein concentration is often elevated in CNS vasculitis and there may be a pleocytosis even in the absence of clinical meningitis. The rise in CSF protein concentration is more marked than that usually seen in MND. The disturbance of anterior horn function associated with the vasculitides including polyarteritis nodosa may respond to immunosuppression.

Other neuropathies

Paraneoplastic neuropathy can mimic MND. Sometimes it is truly an MND-like disorder and on occasion even a Lambert–Eaton myasthenic syndrome (LEMS) has been mistaken for MND. Paraneoplastic disorders are associated with circulating antibodies, for example, voltage-gated calcium channel antibodies linked to LEMS. Sometimes it can be difficult even using electromyography (EMG) always to decide whether a lesion is just neurogenic or whether there is a combination of a neurogenic change and a myopathy. A rare myopathy that causes some difficulty is acid maltase deficiency, which can cause severe respiratory muscle compromise in mobile patients; a condition that is mimicked by a few sufferers of MND. A careful search for upper motor neurone signs may help to avoid diagnostic confusion. When it occurs in adults, lead toxicity can present a picture of a virtually pure motor neuropathy. No case of lead poisoning has been described in terms that could convincingly be recognized as MND. On current evidence, there is no case for treatment of MND with lead chelating agents. A similar controversy has surrounded the link between mercury and MND, but again there is no convincing evidence of an aetiological link. Porphyria and polyarteritis nodosa are causes of a motor neuropathy. Treatment of porphyria with avoidance of the precipitants of acute relapses and treatment of polyarteritis nodosa with immunosuppression can improve disease outcome remarkably. Some of the hereditary motor neuropathies (HMN2 and HMN5) can be mistaken for a predominantly lower motor neurone form of familial MND.

Differential diagnosis of bulbar MND

When bilateral tongue wasting and fasciculation are present, the diagnosis of MND is very likely to be correct. However, when the physical findings both in the limbs and in the mouth are equivocal, a diagnosis of myasthenia gravis must always be considered, as this is an eminently treatable condition. Usually, but not always, a history of fatigable ptosis or diplopia is helpful. These are not seen in ambulant patients with MND. A Tensilon test can aid diagnosis, but interpretation must be cautious as a weak positive Tensilon test can be found in MND. The major difficulty in making a diagnosis of myasthenia gravis is not thinking of the condition. Another rare cause of bulbar weakness and ptosis is the inherited disorder of older adults oculopharyngeal muscular dystrophy, for which there is now a reliable genetic test. A pseudobulbar presentation should activate a search for structural brain pathology such as cerebrovascular disease. It is common for the severe dysarthria or anarthria of MND to be thought of as dysphasia resulting from a stroke. The progressive history and the recognition that the patient's ability to express himself/herself using gesture or writing is totally intact at a time when they are unable to make any sound should clarify whether the problem is dysphasic or anarthric. A proportion of MND patients develop dementia and in rare cases this can be a prominent feature at diagnosis. Frontotemporal dementia may of course present with dysphasia, but this is rare in MND. A combination of dementia and amyotrophy (muscle wasting) with fasciculation can rarely signify a prion protein disorder of Creutzfeldt–Jakob type.

Investigations that aid diagnosis

The diagnosis of MND is a clinical one. The role of investigation is largely to look for other conditions that may mimic MND. These have been discussed above and, where appropriate, diagnostic tests have been suggested. All patients in whom a diagnosis of MND is considered should have nerve conduction studies and these may be combined with EMG. The EMG can confirm electrical evidence of denervation

in marginal cases or may demonstrate denervation in clinically normal limbs, but more importantly, nerve conduction studies which should be normal in MND may point to alternative diagnoses such as a motor neuropathy as seen in CIDP or multifocal motor neuropathy with conduction block (MMN). Elevated plasma creatine phosphokinase (CK) is a non-specific marker of lower motor neurone damage. In other clinical settings it can help with the diagnosis of muscle disorders. CK elevations in MND are more modest than in muscle disease. Generally, values are only increased to no more than 10-fold above the normal upper limit. CSF examination for elevated protein concentrations or pleocytosis may also be helpful in swaying one away from the diagnosis. Having said this, slight increases in CSF protein are seen in MND so that the elevation has to be marked for it to be of significant negative predictive value. Antiganglioside antibodies are found in low titre in many patients with MND and are found more consistently and at higher titres in patients with MMN and CIDP. Paraproteins are found more frequently in the serum of MND patients. Treatment of the paraprotein in these cases does not influence the outcome of MND. Other tests, ranging from looking for antiacetylcholine receptor antibodies to magnetic resonance scanning of the cervical spine, may be appropriate in certain clinical settings as discussed above. Currently there are no biomarkers of a diagnosis of MND.

Diagnosis of MND

Discussion of the diagnosis of MND is an important step in the management of the condition. Nerve conduction tests, an electromyogram, imaging studies and any other tests indicated should of course be completed prior to mention of the words, motor neurone disease. A busy outpatient clinic is hardly a suitable setting for the unhurried imparting of bad news. Following the tests and preferably on the same day, the diagnosis can be discussed with the patient and their family by the doctor and a counsellor with an interest in MND. Any healthcare professional with a knowledge of and interest in MND and the time to be able to discuss matters unhurriedly could develop counselling skills and become an MND counsellor. Patients and their families usually appreciate written information and most appreciate receiving a transcript of or letter about the consultation. The hospice movement in particular and the experience of oncology in general have taught us much about imparting bad news. The principles of breaking bad news range from the use of a private room to fractionating the news so that the patient is not completely overwhelmed by the information and to remembering to emphasize some positive features, for instance, our increasing ability to help all the symptoms of the disease. In our unit, the MND nurse counsellor plays an important role in maintaining contact with the patient and their family, even when they are at home. This outreach function has proved invaluable in reducing the morbidity of the disease, decreasing unplanned hospital admissions and, later on, in facilitating discussions about end-of-life issues As the diagnosis of MND is essentially based on the clinical picture and as there is no one diagnostic test for it, most patients will appreciate the offer of a second neurological opinion. This may be a counsel of perfection as many parts of the world have difficulty with access to one neurologist, let alone two. However, wherever feasible, this course is to be recommended as confident acceptance of the diagnosis by the medical team and by the patient and their family forms the basis of all subsequent management.

Epidemiology

MND is a ubiquitous disorder. The overall incidence and prevalence are greater in men than in women. However, the bulbar-onset type of MND is more frequently seen in women. The average age at first presentation is about 57 years (with only 5% developing disease before age 30 years) and the clinical course is relentlessly progressive over 3–5 years. False-positive and false-negative errors in diagnosis confound accurate study of its incidence, which is variously estimated at between 0.6 and 2.6 per 100 000 per year. The point prevalence ranges between 2.7 and 7.4 per 100 000. Although case ascertainment must play a part in this variability, geographic differences almost certainly account for some of the variation. Even within fairly small areas there can be considerable variation in the incidence of the disease, as shown, for example, by the differences on either side of the river in the Mississippi area of the USA. In the UK, fewer cases than expected seem to occur among the immigrant Asian and Afro-Caribbean population than in the native population. It is unlikely that this could be accounted for merely by differences in the age distribution of the populations. Age-specific incidence figures show an increase in the occurrence of MND into the 70s but with an apparent fall in the 80s and 90s,[18] partly explained by the small population groups in the age ranges. The incidence of MND is increasing especially in the elderly, in whom there is an over-representation of bulbar-onset disease. The occurrence of a type of MND on the island of Guam and on the Kii peninsula and the decreasing death rates from this disease in those areas indicate that the cause of sporadic MND may be exposure to a neurotoxic agent.[19] Several epidemiological lines of enquiry have looked into this but so far no convincing candidate toxin has emerged. Military personnel deployed in the first Gulf War are reported to have a higher risk of developing MND than the general population or than their non-deployed counterparts.[20] It is reported that patients with MND engage in more physical exercise than the general population (for instance, in Italian football players) and it is also likely that they have a stronger previous history of trauma including bony

fractures. These may, of course, be linked as fractures in young people occur more commonly in those engaging in physical activity. A case has been made for abnormalities of parathyroid hormone playing a role in the pathophysiology of this disorder, but the link seems tenuous. Exposure to solvents and, in particular, halogenated hydrocarbons has been associated with MND both as anecdotal cases and in the leather industry. Organophosphate exposure is also postulated as a risk factor. It has been suggested that MND is a late consequence of infection with the polio virus in a situation analogous to the development of an MND-like condition in later life in patients who suffered from polio in younger days. However, the postpolio type of MND is clearly different from ordinary MND.[21] If polio exposure played a part in MND, polio vaccination would have decreased the incidence of the disease – which is not the case. In about 10% of cases of MND, there is a family history of the disorder, suggesting an autosomal dominant mode of inheritance (see earlier). There is an over-representation of statin use in MND[22] and, although data are controversial, a case has been made for a neuroprotective role of dyslipidaemia in MND. Epidemiological information does not indicate an increase in the incidence of MND since the use of statins became more widespread. One study indicated increased MND risk in cigarette smokers. Ongoing MND epidemiology studies may help clarify this confused collection of associations.

Pathology of MND

Prominent degeneration of the pyramidal tracts is seen in the spinal cords of patients dying with MND characterized by loss of motor neurones with changes such as spheroid formation, chromatolysis and neuronophagia of motor neurones. Betz cell loss in the motor cortex is a feature of the upper motor neurone involvement in MND. Astrocytic gliosis can be prominent in a few cases and surviving cells can show accumulations of lipofuscin, which is associated with free radical attack on polyunsaturated fatty acids. Some pathological changes have been described in the posterior columns, the sympathetic pathways and even in Onuf's nucleus, underlining the clinical observation that sensory pathways and bladder innervation are only relatively and not absolutely resistant to the process of MND. A variety of inclusion bodies in anterior horn cells are associated with MND; some of these contain ubiquitin, a housekeeping protein involved in the designation of proteins due for removal. The inclusion bodies include TDP43 containing ubiquitinated inclusion bodies and hyaline conglomerate inclusions containing neurofilaments. Similar abnormalities are found in the brain stem nuclei of cranial nerves that are involved in MND. Those spared in MND, for instance, those of extraocular muscles, are less affected. The upper motor neurone cell bodies and dendritic processes show degeneration and inclusions and there is increased gliosis in layers II and III of the motor cortex and in subcortical white matter, with some changes also being found in the sensory cortex. More widespread changes are found in the brains of dementia patients who die with MND. These include finding intraneuronal inclusions that are ubiquitin positive but tau and alpha synuclein negative.[23] TDP43 is a constituent of the ubiquitinated inclusions in sporadic MND.[12] This protein is involved in RNA processing, suggesting that post-transcriptional genetic changes are involved in the disease process.[24] Tau 1 positive inclusions are found in astrocytes and other tau aggregates in the neuropil in MND patients with dementia. Dementia is an uncommon clinical feature of MND, afflicting up to 15% of patients, although significant cognitive decline can be identified in 35% of patients.[8] Spinal root atrophy is frequently seen at autopsy but involvement of peripheral nerves is rare. Some studies have shown loss of large myelinated fibres secondary to anterior horn cell loss. Biochemical abnormalities are also found in the parietal cortex and in the cerebellum, although these areas are largely clinically unaffected.

Small group atrophy of muscle fibres is seen on muscle biopsy affecting both type I and II fibres with some compensatory hypertrophy of surviving muscle cells. Mononuclear inflammatory infiltrate may also be seen, but whether as a cause or an effect of the disease process is unknown. On antemortem liver biopsy, a variety of abnormalities are linked with MND. These include intramitochondrial inclusions, giant mitochondria and abnormalities of endoplasmic reticulum. Neurofilament accumulations occur in the site of damage in MND. Neurofilament transport, degradation and phosphorylation all seem to be impaired in MND, but their role in disease pathophysiology is unclear.

Aetiology and pathophysiology

Much progress has been made in these areas of research. Some of these are discussed below. Although discussed under separate headings for ease of reading, there are many areas of overlap; for example, xenobiotic compounds may exert their toxic potential through free radical mechanisms and free radical action may be increased by the action of excitatory amino acids. Genetic factors have been considered above (under Familial MND).

Free radicals

Chemical species that are capable of independent existence and contain unpaired electrons are termed *free radicals*. In biological systems, oxygen and nitrogen free radicals, that is, the products of partial reduction of molecular oxygen or nitrogen, are particularly important. One of the enzymes that protects tissues against free radical attack is superoxide dismutase type 1 (SOD 1). This enzyme catalyses

the conversion of superoxide free radicals to hydrogen peroxide. Rosen *et al*.'s finding[9] of mutations in the gene encoding SOD 1 in 20% of families with FALS increased interest in free radicals in MND. Similar mutations are found in only 2% of sporadic MND. However, other abnormalities that represent impaired oxidant metabolism have been found in the spinal cords of patients dying with MND.[25] These include increases in a DNA oxidation product, 8-hydroxy-2-deoxyguanosine, and in some products of protein oxidation such as protein carbonyls. In sporadic MND, the concentration (in the spinal cord) of other antioxidants such as glutathione peroxidase is impaired. These observations suggest that free radical mechanisms may be one means of cell injury in MND. However, the means by which SOD 1 mutations cause damage in MND may not be merely through loss of dismutation activity of the SOD 1 protein but through some new and additional property of the mutant protein – the nature of this additional function remains unclear. It has been reported that mutations in the SOD 1 enzyme change its function from antiapoptotic to proapoptotic. Misfolding of the mutant protein leads to its ubiquitination and deposition in inclusion bodies and it is controversially suggested that all MND may result from misfolding of SOD 1.[26] In the extracellular space, mutant SOD 1 may function as a pro-oxidant by producing superoxide.[27] Mutant SOD 1 also binds early to mitochondria and to the endoplasmic reticulum, suggesting that these organelles are involved in the cytotoxic process.

On the basis of the hypothesis that impaired defences against free radical attack are important in the pathophysiology of MND, trials of therapy with antioxidants have been attempted. Metal chelating agents with antioxidant properties, such as *N*-acetylcysteine have also been used, with unconvincing benefit. Some practitioners have, on purely empirical grounds, recommended that patients take supplements of vitamin C, vitamin E and other commonly available antioxidants. In addition to causing direct damage to nucleic acids, structural support proteins and membrane lipids, free radicals and other reactive oxygen metabolites such as hydrogen peroxide can induce profound changes in intracellular signalling mechanisms. For instance, they can modulate the conversion of the inactive form of NFKB to the active form. They have an effect on gene transcription, for example, as shown by the redox-sensitive regulation of transferrin receptor and ferritin production. In cell culture, these gene dysregulatory effects can lead to neuronal loss by a process of apoptosis. There is therefore much interest in apoptosis in MND. Another cell-signalling compound whose activity is modified by oxygen free radicals is nitric oxide. This can combine with superoxide radicals to form peroxynitrite, a precursor of hydroxyl free radicals, which have a great capacity to cause intracellular damage and consequent cell death. Nitric oxide abnormalities are also linked with abnormalities of excitatory amino acid neurotransmission; this helps to establish a link between the two front-runners in the mechanism of tissue damage in MND, namely, free radicals and excitotoxicity.

Excitatory amino acids

Glutamate is a major neurotransmitter in the CNS. It is an excitatory amino acid which stimulates the anterior horn cell, that is, the main transmitter between the upper and lower motor neurones. Convincing evidence from cell culture studies and experimental animal models demonstrates the toxicity of excessive concentrations of glutamate. This damage is often referred to as excitotoxic damage. The finding of defects in the distribution of glutamate receptors in the spinal cords of patients with MND and the demonstration of a defect of the glutamate transporter in MND support the hypothesis of excitotoxic damage in this disease. The finding of elevated concentrations of glutamate in the CSF of patients with MND also lends support to this hypothesis. The toxicity of glutamate is believed to be mediated via an increase in calcium entry into cells.[28] This may occur through a lack of excitatory amino acid transporter type 2 (EAAT2) action, which results in failure to clear extracellular glutamate.[29] Calcium entry into cells is carefully regulated and can be disturbed by a variety of mechanisms, including free radicals and excitatory amino acids. This, along with the involvement of compounds such as nitric oxide (NO) in both excitatory amino acid neurotransmission and in free radicals, suggests that several mechanisms acting together may conspire to cause anterior horn cell damage in MND. The postulated role of excitatory amino acids in MND led to a search for antiglutamate drugs as treatment for MND. A number of agents have been examined for their antiglutamate properties – amongst these are the branched chain amino acids (leucine, isoleucine and valine), lamotrigine and riluzole. Riluzole shows positive results,[4] which are discussed below.

Growth factors

A whole family of peptide neurotrophic factors is known to affect the growth and survival of human neurones. Some of these have profound effects on human lower motor neurones but have not been shown to influence upper motor neurone survival. The survival of cells deprived of these trophic factors is reduced. Angiogenin is a growth factor involved in promoting primary and metastatic tumour growth. Mutations in the angiogenin gene are linked with being risk factors in sporadic MND and frontotemporal dementia MND. Others that are implicated include ciliary neurotrophic factor (CNTF), brain-derived growth factor (BDNF) and insulin-like growth factor (IGF). Glial-derived

neurotrophic factor (GDNF) has also been of interest in neurodegenerative disorders. *In vitro* GDNF is more potent than either CNTF or IGF at promoting neuronal survival. A decrease in the concentration of growth factors such as CNTF is associated with decreased motor neurone survival.[30] An initial clinical trial of CNTF was abandoned when no benefit was identified and significant adverse effects occurred. Some of the adverse effects could have been foreseen, for instance, through recognition of its interaction with leukaemia inhibitory factor. There was also some doubt as to whether the method of administration of the CNTF would have allowed the drug to reach the site of action, namely the spinal cord – beyond the blood – spinal cord barrier. IGF 1 can induce sprouting of spinal motor neurones and its binding sites are increased in the spinal cord in MND. Much of this spinal binding may be to glial sites rather than neuronal sites. IGF has also been tested in a clinical trial setting and has been found to be helpful in increasing muscle strength in MND without a significant effect on survival.[31] Parenteral BDNF proved ineffective in MND. A new, non-peptide neurotrophic factor with 5HT1a receptor activity (xaliproden) also failed to prolong survival when given along with riluzole in MND. Mutations in the gene encoding VEGF[13,32] and altered activity of the peptide in CSF have been reported in MND.

Viruses

A large number of viruses are linked with MND, but convincing evidence of a causal association is lacking. Agents as diverse as enteroviruses such as the polio virus, retroviruses such as HIV and human T lymphotropic virus 1 (HTLV 1) and even prions are implicated. There is conflicting evidence on the association between polio virus and MND. Enterovirus genome has been reported in the spinal neurones of patients dying of MND. It is suggested that a state of restricted replication may exist in these neurones, a situation akin to that seen in subacute sclerosing panencephalitis (caused by the measles virus) or in tropical spastic paraparesis (caused by HTLV 1). The similarities between the postpolio syndrome and MND have further suggested the possibility of an aetiological connection.

Autoimmunity

An increased incidence of known autoimmune diseases such as diabetes is described in MND. Paraproteinaemias may occur more frequently in MND, also pointing towards immune mechanisms in the disease process. However, in the majority of these patients the paraprotein does not recognize antigens on motor neurones. A guinea pig model of both the lower motor neurone disturbance and the upper motor neurone problems of MND can be induced by inoculation with spinal cord or brain homogenates and neurophysiological changes detected in other species following passive antibody transfer, but the disease is not replicated in these experimental animals after such antibody transfer. The spinal cords of patients dying from MND contain activated T lymphocytes, and immunoglobulin deposits in both the cerebral cortex and the spinal cords at autopsy further implicate dysimmune mechanisms in this disease. Treatments directed against a possible autoimmune disorder, for instance, with cyclophosphamide or with whole body irradiation, have failed to give positive results. A critical analysis of the data on autoimmunity in MND was carried out by Drachman *et al*.[33] In some cases, the paraprotein found in patients with MND has been identified as an *antiganglioside antibody*. Gangliosides are antigens found on neuronal tissues and antibodies against these have been identified in a number of peripheral nerve disorders such as Guillain–Barré syndrome and MMN with proximal conduction block. Low titres of antiganglioside antibodies are occasionally found in MND and, although this may be no more than coincidence or merely a reflection of tissue damage with secondary immunological response, it does implicate immunological mechanisms in MND.

Xenobiotic metabolism

In a number of disorders, it is becoming clear that a combination of genetic and environmental factors may be responsible for disease development. Some of these are well-established examples of the interaction of heredity and the environment. For instance, in the condition glucose-6-phosphate dehydrogenase deficiency, the genetic disorder in itself is not sufficient to lead to haemolytic episodes but cells that are deficient in this enzyme are unable to cope with the additional burden of environmental challenges such as the fava bean. The enzymes that deal with toxins arising from outside the body (xenobiotic toxins) frequently show polymorphisms, that is, there are fast and slow metabolizers of xenobiotic compounds. Most of the body's reserve in dealing with xenobiotic compounds resides in the liver in microsomal enzymes, including the cytochrome P450 system. The idea that a genetically predisposed individual, when exposed to a xenobiotic toxin that their enzyme makeup is unable to detoxify efficiently, ends up getting disease, whereas another individual may escape disease either because they haves the necessary enzyme activity to detoxify or they may not have been exposed to the toxin, can serve to explain the apparent sporadic nature of a number of diseases. This has been implicated in atherogenesis, in Alzheimer's disease, in diabetes and in Parkinson's disease, to name just a few. Heafield *et al*.[34] found abnormalities of the enzymes that metabolize sulfur-containing compounds in MND. These include the enzymes that catalyse sulfur

oxidation, which appears to be impaired, and those that methylate sulfur (thiol methyl transferase) which appear excessively active. Failure to oxidize a sulfur toxin would impair its excretion via the kidney. This, combined with increased methylation, would facilitate entry into central nervous tissue, where the brunt of damage occurs in MND. If the effect were an immediate one, as occurs in, for instance, migraine and chocolate ingestion, the connection would be obvious; but if each event of toxin exposure just resulted in the loss of a few anterior horn cells the overall effect might not be noticeable until late in life. Recent evidence of a role for paraoxonases in MND supports the idea of a complex interplay between genetics and environmental factors in the disease.[35]

Vascular insufficiency

In chronic hypoxic conditions, VEGF production is increased to attempt to overcome the hypoxic state. Finding mutations in the gene encoding VEGF[13,32] suggests that vascular phenomena may play a role in the development of MND. Pentoxifylline, a vasodilator molecule, was tested for clinical effect in a randomized placebo-controlled trial and initial indications are that the drug is not effective in slowing the progression of MND. Changes in spinal blood flow may be speculated to explain the association between physical exertion and MND.

Mitochondrial dysfunction

Structural mitochondrial abnormalities are found at an early stage of MND, in both neural and non-neural tissues.[36,37] The mouse model of MND (both wobbler and the SOD 1 mouse) show early mitochondrial dysfunction. Creatine and phosphocreatine are intricately involved with cellular energy metabolism and these considerations led to a search for a clinically useful therapeutic effect in MND to mirror the improvement seen with creatine use in the SOD 1 mouse. Unfortunately, these studies have been negative. Excitotoxic, apoptotic and oxidant mechanism have all been proposed as the pathway by which mitochondrial permeability is damaged. All are implicated in MND.

Inflammation

A prominent CNS inflammatory reaction is found in MND. Microglia are involved and their inflammatory mediators such as CD11b are overexpressed. COX 2 mRNA expression is increased in MND spinal cords. COX 2 inhibitors were until recently regarded as good candidates for use as treatment in MND. However, the newly identified problems of cerebrovascular disease in patients taking COX 2 inhibitors for rheumatic diseases have stopped these avenues being explored.

Symptomatic treatment

Cramp

This is prominent fairly early in the disease and may affect muscles not normally prone to cramp, for instance, forearm flexors. As the disease progresses, weakening muscles no longer cause painful cramp. Quinine sulfate is anecdotally helpful and, although evidence of its effectiveness is lacking, it is worth trying as a short-term measure. Antispastic medications such as baclofen and tizanidine may help in cramp control. The hepatotoxic effect of tizanidine needs to be monitored, particularly in those patients also taking riluzole. Other aggravating factors such as electrolyte imbalance may also need treatment. In a few cases, phenytoin has been used with good effect, particularly for painless hand cramp.

Fasciculation

Although this is a prominent physical sign in MND, it is uncommon for it to be symptomatic except in patients with benign fasciculation in whom it is more constantly a source of anxiety. Patients with MND are usually more bothered by more disabling symptoms and may not even be aware of the fasciculation, until pointed out by the physician. β-Adrenoceptor blocking agents such as propranolol are occasionally helpful in the few cases when pharmacological treatment is warranted. Low-dose benzodiazepines can also be useful in reducing the discomfort of fasciculation.

Spasticity

When spasticity is marked, it can interfere with the efficient function of limb and bulbar muscles and antispastic drugs, such as low doses of baclofen, can help reduce the spasticity. Dantrolene and benzodiazepines can also be applied but dantrolene is not widely used for this purpose and there are well-founded anxieties about the sedative and respiratory depressant actions of the benzodiazepines. Having said this, their use in some circumstances can alleviate much anxiety and reduce the pain associated with spasticity. The effect of baclofen on jaw clonus and masseter spasticity can be useful in helping chewing and sometimes even speech. In other neurological disorders, spasticity can be treated with intramuscular injection of botulinum toxin. In MND, there is a worry that weakening muscles with botox may help spasticity, but the cost in terms of increased weakness would be even more unacceptable than with baclofen and other antispastic drugs such as tizanidine. As a consequence, botulinum toxin injections are not currently recommended for the treatment of spasticity in MND. Tizanidine may prove helpful in some patients with MND and spasticity, but there are some anxieties about its possible adverse effects on the liver.

Salivary dribbling

Many patients with MND are troubled by this symptom, caused by immobility of bulbar muscles and dysphagia. The discomfort of excessive dribbling of saliva is often greater than that of spasticity or of cramp. It is also more difficult to treat. Patients with MND have decreased saliva production. The cause of dribbling is the impaired swallowing of saliva secondary to muscle weakness. Anticholinergic drugs can ease salivary dribbling by further reducing saliva formation. Drugs such as benzhexol and hyoscine/atropine are generally not well tolerated when given as a tablet. Hyoscine skin patches can be useful and better tolerated. In the author's experience, *oral* administration of 1% atropine eye drops is better tolerated and appears to give good symptomatic relief. The dose required varies but can be only two drops per day. Generally, systemic side effects are uncommon, but occasionally patients will complain of other anticholinergic adverse effects such as constipation, bladder disturbance and blurred vision. Sublingual hyoscine has also been used. Glycopyrronium injections or subcutaneous hyoscine infusions can be helpful in resistant cases. Radiotherapy of one parotid gland has been used when pharmacotherapy has failed, but in such cases the radiotherapy is also usually unsuccessful. Botulinum toxin is increasingly used to reduce saliva formation in those patients who are PEG (percutaneous endoscopic gastrostomy) fed. Botox can spread from the parotid to the pharyngeal muscles and can aggravate pharyngeal weakness, which of course is invariably present in patients with salivary dribbling. When saliva and laryngeal secretions are too thick and stringy to be expectorated, β-adrenoceptor blockers such as propranolol can help. When thick mucus is resistant to such measures, manually assisted coughing techniques and cough assist machines can help with its removal from the airway. Oropharyngeal suction can reduce the consequences of excessive salivary pooling and in some cases can help alleviate the fear of nocturnal choking spells caused by salivary pooling. As salivary dribbling at night can be even more troublesome than during the daytime, strategies that reduce nocturnal salivation can also help, for instance, avoidance of late-night meals or drinks.

Dysarthria

Most patients with MND develop dysarthria or anarthria at some time during disease progression. Sometimes this can happen in the absence of dysphagia but often the two symptoms coexist. In the early stages, speech therapy strategies can help and as disease advances increasing reliance must be placed on communication aids. These can range from a notebook and pen to sophisticated computerized aids, some of which can be linked to voice synthesizers to produce a semblance of the patient's voice. By the time writing aids are needed, dominant arm weakness can clearly add to the disability. The clinical art in dysarthria management is to determine what the most appropriate aid/appliance is for the degree of the patient's disability; for instance, mention of computer-aided speech can dishearten rather than help a patient with mild dysarthria. The assistance of a rehabilitation team including a speech therapist can be invaluable.

Dysphagia

A mild degree of impairment of swallowing occurs in early disease. As dysphagia advances and is coupled with impaired respiratory protective mechanisms (for instance, weakened cough), aspiration pneumonia becomes a serious concern and can cause death in MND. Judicious use of antibiotics can aid comfort. Dysphagia is more marked for liquids and very dry solids. Semisolid foods or foods with puréed consistency are more easily swallowed. Avoidance of very hot or very cold foods/drinks is also helpful. Occasionally, when the bulbar impairment is asymmetric, attempts to swallow can be more successful with the head rotated to one side. Help from dietitians and swallowing/speech therapists should be called upon. In recent years, PEG has dramatically helped feeding patients with severe bulbar MND. Gastrostomies are inserted endoscopically, sometimes using sedation but occasionally with just a pharyngeal local anaesthetic spray. Usually they are well tolerated and, although most patients have severe misgivings about having a gastrostomy, few regret having had one after insertion. PEG does not prevent aspiration and must not be seen as a means of stopping the patient from eating. Food or drink that the patient enjoys or can swallow can be taken by mouth. The patient and his/her family must appreciate that oral intake increases the risk of aspiration pneumonia and provided that they are cognizant of this increased risk, the patient may choose whether or not to eat and drink. PEG probably prolongs survival but is better regarded as a symptomatic treatment that frees up the patient from the chore of swallowing just to make up normal daily intakes of food and drink and avoids nutritional weight loss which would otherwise compound the weight loss caused by the disease process. In some centres, radiographically inserted gastrostomies (RIG) may be used instead of PEG. The 30 day mortality after PEG insertion is markedly increased in those patients whose forced vital capacity is less than 50% of predicted.[38] When recurrent respiratory infections complicate PEG placement, gastric motility-promoting agents such as metoclopramide may be worth trying.

Respiratory failure

This is the commonest cause of death in MND. Dyspnea is a common symptom and the fear of breathlessness

and choking is usually marked but frequently not voiced. Other symptoms include orthopnea, sleep disturbance that cannot be ascribed to pain or depression, early morning headaches and fatigue secondary to carbon dioxide retention. Some patients complain of excessive daytime sleepiness. Respiratory failure most often occurs secondary to respiratory muscle weakness including diaphragmatic weakness. Large-airway obstruction is uncommon. Aspiration pneumonia also accounts for some deaths in MND but the number of these is fortunately decreasing – aided by improvements in speech/swallowing therapists' involvement and by better multidisciplinary team efforts. Some of these patients may have coexisting pulmonary disease such as asthma and others may develop bronchospasm secondary to aspiration or infection. Whether for this reason or for some other pharmacological reasons, salbutamol and other β-adrenergic agonists via inhaler can be helpful in easing dyspnea in some patients with MND. In some patients, β-blockers given to ease other symptoms may be the cause of dyspnea and fatigue. The respiratory drive can be reduced in this group of patients with oxygen supplementation and its indiscriminate use cannot be supported. In selected patients, the judicious use of oxygen (domiciliary oxygen if necessary) supplements by mask or nasal cannulae can help relieve symptoms, as can anxiolytic medication including benzodiazepines. Both approaches carry a risk of respiratory depression but can serve a useful palliative role when patients have been fully informed. In some cases of advanced disease, it may not be appropriate to use antibiotics to treat the dyspnea associated with pulmonary infection. In this situation and in other cases of unremitting dyspnea, symptom control may require opiates, sometimes in combination with hyoscine. The respiratory depressant effect of opiates causes understandable concern in this situation, but this adverse effect should not impair the search for rapid and effective relief of symptoms in the terminal phases of MND. Non-invasive mechanical ventilation is effective as a treatment for palliating respiratory symptoms in MND. One randomized clinical trial involving 41 participants showed improved survival with non-invasive ventilation (NIV) (see review by Radunovic *et al*.[39]). The overall survival advantage was comparable to that with riluzole. Symptomatic patients who have impaired ventilatory capacity, as shown by reduced forced vital capacity or SNP, and who have carbon dioxide retention on blood gas analysis or have nocturnal desaturation on oximetry are suitable for considering NIV. NIV is effective in improving early morning headaches, fatigue, alertness and orthopnea. Any increase in depression caused by the need for assisted ventilation is offset by the sense of wellbeing caused by the mechanical ventilation. Overall depression rates are no different in the ventilated and non-ventilated patients. Nocturnal oximetry can help decide whether NIV is appropriate. Many patients face the problem of Advance Directives for the first time when considering using NIV. Patients with severe bulbar impairment do not tolerate the NIV well. Initially, most patients use the mechanical ventilation systems at night. They need to decide whether they would extend use into daytime hours, potentially even 24 h per day. What are to be the stop rules and how is withdrawal to be effected, for example, with removal of supplemental oxygen, removing end expiratory positive pressure then using a T tube and then using opiates or benzodiazepines to relieve distress and so on? Some patients decide to go on to a tracheostomy with full invasive ventilation. This decision can have a major emotional impact on patients and their carers. Leaving aside considerations of the resource implications of such a decision, patients and their families need to be counselled fully to prepare them to make these decisions. Most patients and their carers indicate a strong wish to make positive decisions regarding resuscitation status, antibiotic use for bronchopneumonia and treatment of multiorgan failure, and want the physician to introduce this topic.

Pain

Pain is common in MND (up to 40%), but this is not generally appreciated and less attention is given to this aspect than it deserves. A doctor's capacity to ease pain is far greater than their ability to ease many other symptoms. For this reason, questioning patients about pain can be a rewarding therapeutic experience for patient and physician alike. Sometimes the pain is caused by cramp but more often it is attributed to the effects of ligamentous strain secondary to weak muscles. Anxiety and fear are common exacerbating factors. In many cases, the cause of pain is obscure. In part, it may arise from subtle abnormalities of central pain pathways. The management of pain in a terminal care setting is the same whether the pain is due to secondary spread from cancer or due to MND. Weakened muscles and ligamentous stretching can lead to partial subluxation and support or orthoses to avoid further subluxation and use of intra-articular steroids and lignocaine can help ease the pain. Weak neck muscles can cause cervical pain and in some patients this can be helped by wearing a cervical collar. The right collar for each individual is one that can be worn comfortably and eases discomfort. Unfortunately, no one collar type fits this bill and the help of a rehabilitation team with experienced physiotherapist and occupational therapist can be helpful.

Depression

Emotional lability is common in MND, particularly in those with bulbar problems. As a result, patients may cry, sometimes inappropriately. However, the disabling nature of the disease can lead to appropriate crying due to either

frustration or depression. Frustration and other affective difficulties such as anger are more prevalent than clinical depression. They can be helped by supportive counselling. When the affective difficulties extend to causing impaired sleep, loss of appetite or loss of self-worth, pharmacotherapy may be needed for the depression. A low threshold to using antidepressant medication needs to be maintained either as the tricyclic antidepressants whose anticholinergic effects may help excessive salivation or as one of the selective serotonin reuptake inhibitors (SSRI), which are safer when, for instance, taken in overdose. Emotional lability which may show as pathological crying or laughter may be treated with the tricyclic drug amitriptyline or by fluvoxamine. Given the nature of the disease, it is surprising that suicide is not more common and perhaps this reflects the success of the support structure that carers and medical services have set up. A counsellor who may be a nurse or other professional with the appropriate knowledge, inclination and communication skills may be able to identify patients at risk of attempting suicide and be able to intervene to prevent it.

Leg weakness

Gait impairment is a frequent presenting symptom in limb-onset MND. Progressive weakness, wasting, fasciculation and cramp cause much morbidity. Weakness about the ankle causes most marked early morbidity. Foot drop can be managed in the early stages by physiotherapy, sometimes using foot drop splints. More sophisticated orthoses are sometimes needed. The decision on progressing from ambulant mobility to wheelchair needs to be made carefully and is never easy from a psychological viewpoint. A multidisciplinary team is more likely than an individual clinician to persuade a patient of the wisdom of this transition. Few MND patients have arm strength good enough to allow self-propulsion of a mechanical wheelchair. Some will benefit from an electric wheelchair but these too may require an attendant, as powered chairs can be heavy and difficult to lift, for instance, in and out of cars. Mobility inside the home also needs attention. Patients may be fine to walk on level ground but unable to go safely up and down stairs. This can require single-level existence, stair-lift or even a through-ceiling lift. Not many patients want the disruption of a through-ceiling lift but information from a disability team may persuade them to accept this.

Arm weakness

Hand weakness with wasting of muscles innervated by the T1 nerve root can be the first sign of MND. It is usually asymmetric and even with profound wasting in several myotomes, arm tendon reflexes are usually preserved and even exaggerated, indicating a combined upper and lower motor neurone lesion. Fine motor tasks are impaired and the patient may complain of cramp in the early stages. The combination of anarthria and dominant hand weakness is a particularly disabling one. Communication is severely hindered. In this setting, computer-aided communication with bespoke switching and pointing devices comes into its own. Physiotherapy and occupational therapy involvement becomes more important as the weakness increases. Passive exercises to prevent contractures and simple splints to aid comfort by maintaining neutral postures can help. Weak limbs with wasted muscles are prone to suffering secondary problems such as entrapment neuropathies of nerves previously cushioned by a mass of muscle. Avoidance of pressure over the elbow or the carpal tunnel is necessary. They are also prone to subluxation at several joints, for instance, at the shoulder when the arm is a flail dependent limb. Adequate arm support with appropriate local measures such as intra-articular steroid and local anaesthetic injection may be warranted. Splints and arm supports must be customized to maximize the efficient use of the weak arm.

Advances in drug treatment

Riluzole

Riluzole is a glutamate antagonist that acts on voltage-gated presynaptic sodium channels, inhibiting glutamate release and also increasing glutamate reuptake from the extracellular space. A large randomized dose-ranging multicentre study across Europe and the USA[4] demonstrated increased lifespan in patients taking riluzole compared with those on placebo at a dose of 100 mg per day. Side effects included potentially serious impairment of liver function, mild anaemia, leukopenia, malaise, gastrointestinal upset and dizziness. A Cochrane meta-analysis has shown the mean prolongation of survival to be 2–3 months after 18 months of treatment at a dose of 100 mg per day in patients with probable or definite ALS, with symptoms for less than 5 years, good ventilator reserve (FVC >60%) and age less than 75 years at the start of treatment. This represents a survival advantage of 9% at 1 year and the number-needed-to-treat to prolong one life is 11. From a scientific viewpoint, this development is exciting as for the first time a trial has shown significant benefit from a pharmacological intervention in MND. However, from a clinical viewpoint the trial results are less impressive but nevertheless encouraging. Few patients who start on medication have to give up owing to side effects. A few stop because of abnormal liver function and some give up when swallowing deteriorates to the point when tablets become a chore and they do not want to crush tablets and inject a suspension down a PEG tube. Riluzole is useful in offering hope to patients and their families and in providing a weapon with which to

combat the disease. This aspect of its effect and its impact on quality of life are not easily measurable.

Growth factors

Insulin-like growth factor or IGF 1 is a neurotrophic substance that has been shown to increase muscle strength in MND without any effect on survival.[31] This neurotrophic substance has been used widely outside the UK. Its effect may be mediated via a mechanism involving growth hormone. Other growth factors such as ciliary neurotrophic factor, brain-derived growth factor, glial-derived neurotrophic factor and xaliproden have been tried in MND and have failed to show clinically meaningful improvement.

Clinical trials of other agents

A trial of lithium carbonate as treatment for MND is under way in the UK and in the USA. Clinical trials that have failed to show positive response in MND include *N*-acetylcysteine as a chelator, branched-chain amino acids as inhibitors of glutamatergic transmission, the muscle growth promotor creatine and the vasodilator oxypentifylline. Drugs that block the presynaptic production of or release of glutamate may be neuroprotective. Gabapentin may be one such drug that has been used in MND. Its more conventional use is in pain management and epilepsy, where its mode of action is unknown. In a trial in MND, no significant benefit was found with gabapentin treatment, suggesting that the drug should not be used in this setting. A US trial of topiramate in MND failed to show benefit. Minocycline attracted interest among patients with MND[40] and findings of the *in vitro* effects of antibiotics on motor neurone function suggested this to be a fertile area for further study. However, there is no benefit from minocycline use in a larger study. Cox 2 inhibitors were similarly interesting until the recent worries about their vascular effects. Vitamin E, TCH346, tamoxifen and celecoxib have failed to show a positive response in clinical trials. Stem cell therapy holds more hope for many patients. Stem cell treatments seem promising as areas for future development and may not be far off translation into clinical practice.[41]

Multidisciplinary team approach

MND is an uncommon disease. The average general practitioner will see only one or two cases in a lifetime. As seen above, it is a disease that progresses rapidly and in which the patient's disability needs require addressing quickly before progression makes the measures ineffective and redundant. These requirements of prompt intervention, anticipation of future difficulties and awareness of the sources of help require a specialist team of healthcare professionals. Having said this, there is only weak evidence in favour of the MDT approach and that evidence favours its use to improve psychological wellbeing.[42] Several ways of delivering care are possible but a multidisciplinary approach has advantages by extrapolation from other disorders. The geographic area covered by an MND team or clinic will vary according to local needs and availability of resources, but the larger the area covered, the greater is the need for an outreach service that avoids making patients and carers travel long distances to hospital-based services. The core structure of an MND team should ideally include a consultant with an interest in MND and its rehabilitation needs (in the UK, usually a neurologist), a nurse counsellor, a point of quick contact that the patient and their family can access (e g. a nurse counsellor), a physiotherapist, an occupational therapist, a speech therapist, a dietician and a social worker (in the UK). Many others also have a contribution to make and can be involved by the core team as necessary. For example, a gastroenterologist's help is needed to insert a PEG for feeding, an orthotist may be needed for simple appliances and the assistance of a specialized rehabilitation centre may be required for patients with marked disability needs. Liaison with the community services is critical and requires one member of the MND team to maintain contact with community disability teams, general practices and social services departments. These comments apply to the health delivery system in the UK, but the general principles are equally applicable in other countries. The speed of response is emphasized – the time to provide a stair-lift is when the patient is still able to use it and not when they are bed-bound.

End-of-life issues

The hospice movement and the cancer services generally have made a contribution to the management of the terminal phase of MND. They can help with symptom management by liaison with the GP and the MND team and are increasingly involved in the early stages of the disease. In an audit of hospice care, 94% of patients dying with MND were judged as 'peaceful and settled' at death in the hospice. Some will have a fairly short period of deterioration, usually at home, and the patient and their carers may not wish for any outside help/intervention/interference. Many will welcome offers of help, whether the patient chooses to stay at home or comes to a hospice or a hospital ward. By this stage of the disease, treatment objectives and priorities must be clearly established, jointly with the patient and their carers. Usually this is a decision to relieve distress and discomfort. Judicious use of opiates and benzodiazepines helps to relieve distressing symptoms and, although there are well founded worries about the respiratory suppressant effects of these drugs, a prevalent medical view is that these worries must not stand in the way of symptom relief accompanied by a full explanation of the situation to the

carers and the patient. Ideally, these discussions should have been carried out before a crisis is reached so that the physician is aware of the patient's and their family's stance on this.

Much of the press and lay interest in end-of-life issues in MND has centred on voluntary euthanasia and physician-assisted suicide, and although these are important topics for society to give the medical profession clear guidance on, the concept of end-of-life issues is a wider one. It includes non-medical areas, for example, making a will, and may include, for instance, patients making their peace with estranged relatives. The patient may choose to discuss different aspects with different team members. They may wish a social worker or a counsellor to be involved in family reconciliations but a doctor in discussions on ventilatory support. MND care must take account of the cultural and psychosocial needs of the patient. Within the constraints that this places, early discussion of major management decisions is desirable, particularly for interventions such as PEG and ventilatory support. Advance directives on such interventions should be reviewed every at least every 6 months, as evidence shows that MND patients may change their minds over this period of time. A mentally competent patient is clearly able to make judgments about what is best for them. Mental capacity is usually satisfactory in MND except in those patients with frontotemporal dementia.

Physician-assisted suicide (PAS) remains illegal in the UK and in many other jurisdictions. Patient pressure is increasingly asking for the law to be relaxed, some patients even choosing to travel abroad to seek doctors' help in their suicide. Some of these patients are asking for clarification of what would constitute an offence for which their relatives may face prosecution. One survey of doctors' views showed that a significant minority support a change in the law to accommodate PAS. Others see the pressure for PAS as a failure of a medical system that cannot relieve a patient's distress sufficiently to deter them from such a course. Yet others are worried about the proper implementation of safeguards to protect vulnerable patients. The UK House of Lords has previously debated draft legislation and turned down the acceptance of PAS. Currently, society accepts and permits application of the principle of 'dual effect' in medical practice in palliative care. Doctors may give increasingly larger doses of medication including opiates and benzodiazepines to relieve patients' distress in a terminal disease such as MND, accepting that a second consequence of this action is respiratory depression and possibly, acceleration of death. However, the primary motive remains one of relieving distress and not accelerating death. Any crossing of the current boundaries must examine the concept of the 'slippery slope' to determine whether permitting PAS would necessarily lead, in steps, to other interventions that are currently undesirable or abhorrent.

Key points

- Early diagnosis and speedy multiagency interventions facilitate good palliative care in MND.
- Many MND-mimic disorders are eminently treatable.
- Riluzole and non-invasive ventilation prolong survival in MND.
- Early involvement of palliative care agencies helps with timely interventions such as PEG tube placement.
- Superoxide dismutase 1 mutations cause 20% of familial MND.
- End-of-life issues and symptom relief are inextricably linked.

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CHAPTER 69

Control of chronic pain

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Introduction

Pain is a percept defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1] Most health conditions associated with ageing carry a substantial burden of pain. Pain is always subjective as there is no way to validate objectively a patient's pain report. Every day acute pain occurs as an early response to a strong mechanical, thermal or chemical noxious stimulus such as experienced after an injury or surgery, where it may be immediate or delayed by hours or with infection that develops over hours and persists for a few days. Acute pain demands attention and an early response in order to obtain pain relief and protection from further tissue damage. Acute pain is easily recognized by clinicians, who are well trained to seek a cause so that treatment can be implemented without unnecessary delay. Acute pain affects about 5% of older people at any point in time.[2] Often self-limiting, acute pain usually resolves either spontaneously or with specific treatment often directed at the cause of the pain such as when immobilizing a fracture. The older patient presenting in acute pain should not be taken lightly.

In a proportion of cases, pain does not resolve spontaneously, with the patient progressing through a subacute phase to chronic pain. At this stage, pain no longer serves a protective role and is associated with social, functional and psychological consequences. Chronic pain is best defined as pain persisting beyond the period of normal recovery.[3] By consensus, this has been taken to be 3 months if pain has an ongoing cause. When chronic pain has accompanying physical, psychological and social consequences, multidisciplinary management strategies are required. Common sense dictates that in this situation the source of chronic pain should be understood and that investigations and treatments previously used but found to be ineffective be documented to ensure nothing remediable has been missed. There is, however, still a tendency to 'medicalize' the patient with chronic pain at the time of presentation to a new treatment team, with further investigations and repeated treatments, often with an over-emphasis on pharmacological and anaesthetic approaches. It becomes the managing physician's role in this context to recognize that curative approaches are no longer feasible or acceptable to the patient and that it is time for a symptom management approach to be adopted, aiming to reduce pain to tolerable levels, enhance the individual's coping strategies and minimize any pain-related handicap. This chapter summarizes pertinent data in this field and presents a model for the assessment and management of chronic pain in older people.

Pain and ageing

Overall, the prevalence of persistent pain increases with age and peaks between 45 and 65 years of age in males and between 65 and 75 years in females.[4] Prevalence estimates of persistent pain in older adults range between 25 and 50%. Among nursing home patients, the reported prevalence ranges are generally wider, being reported to be between 27 and 83% in one study.[5] This wide range, especially in residential care settings, indicates the difficulty in addressing a subjective experience in a population with a high prevalence of comorbidities, particularly those associated with cognitive and communication difficulties. This has been the focus of some published management guidelines.[6] There are also methodological differences that partially explain these variations.[5,7] Thus, high prevalence studies often use surrogate measures such as carer opinion and analgesic use to support the contention that the person is in pain. In community samples, the variation may be the result of using biased samples, different time windows for pain (e.g. pain in the last week or month versus all-of-life pain) or summing of pain experienced at different body sites. However, most of the variability is

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more convincingly explained by using different criteria for determining the effect of pain in interfering with desired functional outcomes for the individual.

Most of this reported pain prevalence, however, is dictated by the high prevalence and persistence of musculoskeletal disease, especially degenerative joint disease in the spine, limbs, hands and feet. This is an example of somatic nociceptive pain. Other pain states are also important to older people although they may have less impact on prevalence studies because of their relatively limited duration, perhaps 1 year or less, compared with degenerative disease which lasts for decades. Visceral pain is characterized by poor localization and may be associated with strong emotional and autonomic responses. The principles for management of chronic visceral pain are the same as for somatic pain, with the rare exception of surgical lesioning of the posterior instead of the lateral columns of the spinal cord if pain is intractable to all treatments. Many of these conditions are described in detail in other chapters. A summary classification of clinical pain states into nociceptive, neuropathic, mixed and other, together with some examples that affect older people, is given in Table 69.1.

One of the most important pain-associated disease states of short duration in older people is cancer, as over half of cancer patients are aged 60 years or over and more than 90% experience pain with their disease. About 20% of cancer patients have pain associated with their treatment. Cancer pain can be nociceptive, neuropathic or mixed in type.

Other chronic neuropathic pain conditions that affect predominantly older people, albeit in smaller numbers, include peripheral nerve conditions such as post-herpetic neuralgia, with at least 50% of affected people aged over 70 years experiencing 1 year of pain and painful peripheral neuropathy, with diabetes as the commonest cause in 30% of cases. Neuropathy occurs in ~50% of diabetic patients and pain is a feature in about 20% of this group. Other causes of peripheral neuropathic pain include surgery, radiculopathies and nerve compressive syndromes, including vertebral canal stenosis. Central neuropathic pain after stroke, another age-related disease, occurs in 8% of stroke-affected persons. Trigeminal neuralgia, although relatively less common, is also observed more often in older people.

Table 69.1 Classification of chronic non-cancer pain.

Type of pain	Definition	Examples
Nociceptive pain	Pain derived from stimulation of pain receptors. It may arise from trauma and mechanical causes, inflammation, degenerative and other pathologies	Low back disorders (vertebral compression fractures, facet arthropathies, spondylosis) Rheumatoid and other inflammatory arthritides Visceral pain, e.g. chronic pancreatitis, cholecystitis, prostatitis, recurrent myocardial ischaemia
Neuropathic pain	Damage to the peripheral and/or central nervous system	Post-stroke pain syndromes, diabetic neuropathy, post-herpetic neuralgia, carpal tunnel syndrome, trigeminal neuralgia, radiculopathy, vertebral canal stenosis, surgery
Pain related to psychological or psychiatric disorders	Psychological/psychiatric factors are judged to play a major role in the onset, severity and maintenance of pain	Pain disorder (DSM4)
Pain of uncertain pathogenesis		Recurrent headaches, fibromyalgia, irritable bowel syndrome Complex regional pain syndrome type 1

The biopsychosocial concept of chronic pain

Pain is never a consequence of age alone and it is rare for it to have an entirely psychological genesis at any age. Many people cope with persistent pain and do not seek medical intervention as they perceive that the burden of treatment is greater than the burden of disease. In nearly all situations where chronic pain is a problem for the patient, there is evidence of nociceptive and/or neuropathic pathophysiology associated with maladaptive attitudes or beliefs and inappropriate behaviours operating in a potentially adverse social milieu. The current concept of chronic pain is that cognitions (appraisal of the situation and beliefs about pain and its treatment) are interposed between noxious stimulus input into the central nervous system and behavioural outcomes. Thus, an approach that targets only the pain stimulus and its nociceptive and neuropathic pathways, without taking into consideration the individual's appraisal of the situation and the role of their environment and support structures, may lead to suboptimal outcomes.

Chronic pain is frequently associated with mood disturbance. Epidemiological data based on community samples suggest that about 10% of older people aged over 70 years have depressive symptoms or have been treated for depression.[8] The prevalence of anxiety is less well defined as the instruments used to determine affective disturbance overlap on these domains. In pain clinic samples, older patients generally express less anxiety than their younger

counterparts. Other mood states, which are rarely pursued during clinical assessment, include frustration, anger and demoralization. There are validated psychometric instruments that may be used to explore these other facets of mood disturbance in older people, such as the Profile of Mood States,[9] but they have not been used in epidemiological studies.

There are multiple belief system constructs postulated in the psychological literature that might explain modulation of pain behaviours. The commonest approach is to consider coping strategies or their converse, catastrophic thinking, with feelings of despair, fear or helplessness. Other concepts, however, may also be relevant, such as locus of control, stoicism and fear avoidance. The relationship between pain and gender has not been clearly defined in older people, although certain conditions occur more commonly in elderly females, such as joint pain, chronic widespread pain and fibromyalgia. Chronic pain is more likely in widows living alone. The effects of ethnicity on pain expression in older people remains underexplored.

Age-related changes in the nociceptive system

Pain threshold is the level of stimulus intensity (mechanical, thermal, chemical or electrical) that a subject first perceives as being noxious. Pain tolerance is the maximum amount of a noxious stimulus that a subject can bear. The trend of psychophysical studies suggests that the sum of physiological changes in older persons results in higher pain thresholds, especially to very brief noxious stimuli, but lower pain tolerance.[10] This increase in threshold might suggest a compromise of the warning function of pain by shortening the time between perception of pain and the onset of tissue damage in the acute setting and under-reporting of mild pain so increasing the risk of undiagnosed disease or injury. On the other hand, decreased pain tolerance might lead to an increased vulnerability to persistent pain.

In addition, in the elderly, noxious stimuli delivered at low frequencies of around 0.2 Hz are capable of showing temporal summation, meaning that for the fifth repeated stimulus a noxious stimulus is rated to be more painful when compared with the first stimulus. This phenomenon only occurs in the young at higher frequencies, suggesting amplified or more severe pain in older people once stimulation is under way. In addition, it has also been demonstrated that after prolonged noxious stimulation endogenous pain modulation mechanisms in the older person are not activated to the same extent as in younger adults. The effect of these functional changes in experimental pain on the experience of clinical pain in older people is not yet completely understood, but will become clearer as further studies of these phenomena are undertaken.

The clinical literature is supportive of the notion that the older person feels less pain for a given level of nociceptor stimulation, but it is difficult to control for severity of disease, as attested in a largely anecdotal surgical literature in conditions as varied as analgesic requirements during surgery, fracture, peritonitis and ischaemic heart disease. There is also support for the view that severe clinical pain is less well tolerated in older people. Once an older person reports pain, they should be believed and managed accordingly. However, the converse may not be true. The absence of pain in an older person should not be interpreted as absence of pathology.

Assessment

When an older individual initially presents to a health practitioner with acute pain as a major symptom, it is appropriate for the clinician to be focused on the pathology causing the pain and then on the provision of symptomatic relief. However, when pain becomes chronic, the focus shifts to outcomes pertaining to quality of life, such as maintenance of independence and the balance between pain relief, increased function and side effects of treatments.

The ageing process is associated with multiple social, personal and health related losses. Persistent pain may be only one of the factors that modulates the wellbeing of the patient. Establishing how persistent pain affects overall quality of life is important in planning treatment. In some situations, when the patient is well known to the physician over many years, the relevance of the pain problem can be easily recognized and managed by the physician acting alone or in concert with an appropriate allied health professional, such as a physiotherapist. However, if the pain problem is complex and limited information is available to facilitate construction of a comprehensive management plan, even with or despite the input and best intentions of different therapists acting independently in the past, a multidisciplinary approach to management is to be preferred. In practice, the skills of a doctor, a psychologist and a physiotherapist, all experienced in the care of older people, are complementary and sufficient to allow for a broad multidimensional picture to be assembled on each patient. A nurse, occupational therapist and pharmacist may often contribute other perspectives to the assessment. The total time commitment in a complex patient may be several hours.

Domains of assessment

Assessment of chronic pain in the older person is similar to that in the younger person. It is best based on self-report, either through face-to-face interview or by questionnaire. Common problems in older people making the assessment more difficult are visual, hearing and cognitive impairments. There may be overlap of symptoms of comorbid

Table 69.2 Summary of assessment domains.

1	*The medical aspect:*
	What are the pathological processes that have resulted in the present pain syndrome?
	What are the patient's comorbidities and how are these likely to influence the assessment and treatment processes?
	Is the pain primarily nociceptor in origin, neuropathic, a combination of the two or unexplained?
	Is specific disease management or a symptom management approach required or both? Are there features to suggest more sinister pathology (red flags)?
	Is polypharmacy an issue complicating the management of the pain problem?
	What factors are likely to limit compliance?
2	*The functional aspect:*
	What functional implications are there for the patient from the pain as opposed to the pathology underlying the pain and other comorbid disease states?
3	*The affective aspect:*
	Is the pain associated with depression, anxiety, anger or other mood disturbance?
4	*The social aspect:*
	What impact does the pain have on social relationships and are relationships maintaining the chronic pain syndrome?
5	*The cognitive aspect:*
	What are the patient's beliefs about the cause, prognosis and treatment options for the pain?
	How are these factors interacting with their pain?
	What agreed simple measurable goals are there that will determine the success or otherwise of any intervention?
	Is general cognition failure interfering with assessment, coping or medical management?
	Is pain or its treatment interfering with memory and the ability to think?

medical conditions further compounding the difficulties in pain assessment in older people. A summary of assessment domains relevant to the pain problem is shown in Table 69.2. Details on assessment tools validated for use in older people that cover most of these issues are contained in an international consensus statement (2007),[11] the American Geriatrics Society Panel on Persistent Pain in Older Persons statement (2002)[12] and guidelines for the assessment of pain on older people by the British Pain Society and the British Geriatric Society (2007),[13] bring an additional clinical perspective to this task.

The medical/physical assessment

A thorough pain history should include information on the onset, duration, site, radiation, severity, character and temporal characteristics of the pain. The last includes such factors as whether the pain is intermittent, lasting for seconds to several days, paroxysmal (repetitive shocks) or continuous. Sometimes the frequency of intermittent pain is very revealing, especially if it is very brief and occurring only every few days, as this suggests that other factors contributing to the patient's distress are more relevant to their assessment. Precipitating, aggravating and relieving factors are very helpful in determining both the site of pain and its cause. There may be multiple sites of pain which are of differing pathogenesis such as seen in patients with nociceptive pain from degenerative disease of the spine combined with radicular pain in the limb of neuropathic type. Sometimes the interaction is from two distinct pathologies such as central neuropathic pain from stroke and degenerative disease of a major joint. A pain diagram may give a better representation of the type and distribution of the various pains. There are brief screening instruments which help differentiate nociceptive pain from neuropathic pain based on the pattern and quality of pain, but none are sensitive or specific enough, or have been validated independently in older people, to allow for confident use in the clinic. Some patients will deny the presence of pain but readily accede to experiencing soreness, hurt, an ache or some other descriptor that healthcare professionals would accept as being unpleasant or painful.

The severity of the pain rarely helps differentiate the type of pain which is present but is often useful in determining the success or otherwise of interventions. It may also give an insight in the patient with a long, complex, disjointed history to ask whether the pain is better, worse or the same now as it was at the time of its onset years before, bearing in mind that memory for pain is poor and correlates better with current mood state than previous pain records. It must be recognized that severity is only one approach to measurement of pain.

Severity is best determined using a simple instrument such as a 10-point scale of pain with zero representing no pain and 10 representing the worst possible pain imaginable. Some patients do better with a more limited word descriptor scaling instrument that essentially represents mild, moderate and severe pain. Older people do less well with visual analogue and pictorial scales. The important point is that the physician should be prepared to use a variety of scales and settle on the one that is best understood by the patient. Once this has been achieved, it is relatively easy to obtain a record of pain now, pain at worst, pain at best and average pain over a chosen time frame, which is conveniently represented in the Brief Pain Inventory (BPI).

These scales focus on the sensory dimension of pain. Unpleasantness scales have never been validated in older people. The McGill Pain Questionnaire (MPQ) evaluates the sensory, affective and cognitive aspects of pain. It has been validated for use in older people. It contains a five-point severity scale, the Present Pain Intensity and a

variety of descriptors in sensory, affective and evaluative domains, which are most useful in building a picture of the pain type. Examples of word descriptors include aching, burning, shooting, cruel and exhausting. The short-form MPQ, also validated in older people and which concentrates on sensory and affective domains, is simpler to use than the full instrument and is easily used in a clinical setting. The authors' preference is for the Gracely Box Scale (GBS),[14] as it combines a numerical rating scale, a verbal rating scale and anchor points directly based on psychophysical experiments matching words to the intensity of physical stimuli, although its efficacy in older people has not been formally documented and the verbal rating intervals have only been validated psychophysically in young adults. Other disease-specific instruments and non-verbal measures based on facial expression are available.

The history should also include exploration of current and previous treatments, including complementary and alternative therapies and why they may have been ineffective. For instance, too rapid introduction of a medication leading to cessation of treatment prematurely because of otherwise avoidable adverse events, inadequate amounts of medication at each dose point, inappropriate timing of medication or inadequate duration of treatment trials, poor tolerance and poor compliance often underlie the brief report that the treatment was not helpful. Past physical and invasive treatments should also be recorded with similar attention to detail to ensure they were appropriately administered. It is our experience that the medication list and schedule of use provided by a referring physician rarely matches the medications placed on the table by the patient.

The physical assessment should focus on the site and nature of the pathology, including deformity, degree of firmness or fluctuance of swellings, adherence to adjacent tissues and tenderness, in addition to posture, flexibility (active and passive range of movement) and crepitus of joints, dexterity of movements and gait and direct evidence of nervous system involvement with a focused neurological examination, especially with respect to detection of altered primary sensory perceptions. This includes the presence or absence of hypoalgesia, representing peripheral or central denervation and hyperalgesia, hyperpathia and allodynia representing a state of hypersensitivity mostly due to central sensitization at a spinal cord level. This may occur following injury to both somatic and nervous system elements. It should be remembered that this hypersensitivity is associated with enlarged receptor fields resulting in pain, both spontaneous and evoked, being experienced well beyond the limits imposed by the anatomical distribution of nerve roots, plexuses or peripheral nerves that innervate the affected body part. Autonomic activity and myofascial trigger point activity are generally attenuated in older people and therefore less prominent. Observation and recording of spontaneous movements and non-verbal pain behaviours during the physical examination are also often helpful.

Of fundamental importance in determining outcomes of management is the ability to perform preferred everyday activities, perhaps best assessed in the individual's usual environment. An effect of pain on personal activities of daily living such as showering, grooming, dressing, feeding and toileting is unusual, but instrumental activities of daily living such as shopping, cooking, home care and transportation are often impacted. Effects on discretionary and vocational activities that often provide social support to the isolated individual who lives alone and even the ability to attend to healthcare, are often very relevant to independent older people. Measuring distance walked and time taken is perhaps the most simple and revealing. The best outcomes are usually those that improve function. A wide variety of instruments, both self-report and performance based, have been validated for this purpose in older people and should be used to assess progress and reassess goals at appropriate intervals. A full physical, functional and environmental assessment may need to be undertaken over more than one appointment, particularly for more frail individuals.

Following this initial assessment, causes of pain that need urgent or specific interventions should be attended to first. If the exact pathology cannot be accurately ascertained, however, it should not be relentlessly pursued if there are no features to suggest a deleterious outcome. Often a long history without progression of symptoms or underlying pathology becoming apparent is reassuring. 'Red flags', indicative of severe underlying disease, include weight loss, chronic ill health and a history of other systemic illness such as malignancy, progressive neurological deficit, progressively worsening pain and increased intensity of pain at rest, and all need timely follow-up. The recurrence of severe pain in an individual whose pain was previously well controlled also warrants careful reassessment. Where there is good correlation between the clinical findings and radiological studies, specific management of the underlying pathology may be considered, for example, joint arthroplasty. Age *per se* should not be taken as an excuse to withhold beneficial surgical management. Another caveat operative in chronic pain is that functional and clinical severity may not correlate with the severity of pathology on imaging. This especially applies to radiographic assessment of osteoarthritis of the hips and knees and magnetic resonance imaging of the lumbar spine. Lumbar spondylosis and vertebral canal stenosis are common findings in the aged spine, even in asymptomatic individuals, and these findings should not become the focus of treatment unless the clinical assessment correlates with the radiological findings.

The psychological assessment

The psychological assessment should take into account affect, pain-related cognitions and pain-related behaviours. The assessment of depression and anxiety must take into consideration the changes associated with normal ageing, frailty and the effects of comorbidities. These symptoms often overlap with those observed in depressed patients, such as altered sleep and appetite. The Geriatric Depression Scale, which largely focuses on attitudes rather than somatic symptoms, remains the gold standard assessment tool. Others, such as the Beck Depression Inventory (BDI) and Centre for Epidemiologic Studies Depression Scale (CES-D), have also been widely used with older people. Two anxiety scales used with older people are the Hospital Anxiety and Depression Scale (HADS) and Spielberger's State–Trait Anxiety Inventory. Establishing the temporal relationship between the pain problem and the mood disorder is important. Treating a primary affective disorder requires a different approach.

Adaptive and maladaptive pain-related cognitions, in the form of beliefs, thoughts and appraisals, must be identified. These may relate to beliefs surrounding the meaning of the illness, the types of treatment that are available, the amount of control one has over pain and the strategies that one can use to cope with pain. Some cognitive factors that can lead to poor outcomes include beliefs that the severity of pain correlates with the severity of the underlying illness and perhaps therefore severe ongoing pain represents an undiagnosed cancer or severe ongoing damage. Other maladaptive beliefs are that only medications or an operation will resolve the pain or that all physical activity should be limited until the pain resolves. Pain-associated behaviours include expressions of pain such as grimacing or rubbing, lying down in company and avoidance of activities. This may include pain-related fear of movement (kinesiophobia) and avoidance of everyday activities (fear avoidance). An undue emphasis on passive strategies (e.g. massage, traction and heat) and over-reliance on others (e.g. doctors) to bring the pain under control is maladaptive. Some individuals have unrealistic beliefs regarding the efficacy of doctors or of prayer. Catastrophizing, for instance, feelings of fear and helplessness, is the most maladaptive behaviour. Conversely, cognitive factors that can lead to better outcomes include high self-efficacy (a person's positive appraisal of their ability to undertake coping behaviours), a belief that active strategies (e.g. relaxation exercise) are helpful and a belief that the patient is able to control or modulate their own pain. Another approach to these cognitive factors is that they represent either an (adaptive) internal locus or (maladaptive) external locus of control.

The social assessment

Living alone and widowhood are factors known to affect pain report and outcomes adversely.[15] Conversely, the concern and support of relatives are often helpful in the rehabilitation of chronic pain sufferers. There is often a fine line between appropriate family support and being oversolicitous for the patient's welfare. For example, if a spouse insists on undertaking activities for the patient this will lead to deconditioning and possibly exacerbation of musculoskeletal pain. An expectation of solicitous behaviour on the part of the patient can also result in social conflicts. The evaluation should also consider the possibility of carer stress, which may contribute to the severity of the patient's symptoms or their impact. The physician needs to make a judgement as to how much of the assessment should take place with and without family and carers being present, bearing in mind that successful outcomes are more likely if carers are actively involved in management strategies.

Assessment of pain in dementia

Given the high prevalence of chronic pain and dementia among older people, these two problems are likely to coincide. A brief cognitive screen is therefore advisable in the majority of older people presenting with chronic pain. Indeed, it is not uncommon for a patient who presents with an exacerbation of a previously known and controlled pain to have new onset cognitive impairment as the cause. Conversely, clinical studies suggest that under-treatment of pain in patients with dementia is common and observational studies have shown that patients with dementia tend to be given less analgesia than cognitively intact individuals with the same pathology, for instance, after femoral neck fractures.[16] There are many different types of dementia and even within a single diagnostic group individuals differ with regard to their cognitive and communication abilities. In recent years, as interest and concern in this area have increased, there have been numerous studies directed at improving our understanding of this combination of conditions.[17]

Dementia is usually associated with impairment of memory, affecting the ability to give a history of pain. Cognitive impairment is often associated with language impairment; for example, aphasia in vascular dementia and increasing paucity of vocabulary in advanced Alzheimer's disease. Multiple observations may be required for accurate and reliable diagnosis and an informant history should be sought. The inability of an individual to report pain does not exclude the possibility that they have pain of a severity to warrant treatment. The problem of severity assessment increases as the dementia worsens. For patients with

dementia who are communicative, the scales listed above are still relevant. There is no consensus as to which scale is the most appropriate, although there is some suggestion that word descriptor scales are able to be completed more frequently than numerical rating scales As with the cognitively intact patient, it is best to try a number of different scales and select the instrument that the person appears to manage best. In this way, most people with moderate to severe dementia are still able to have their pain assessed in the normal way.

In non-communicative patients, observer interpretation of pain behaviour becomes very important. Some features include change in facial expressions, such as brow lowering, orbit tightening, upper lid raise and eyelid closure, and others relate to vocalizations, guarding or protective posturing and general change in motor activity. Measures for these behaviours continue to be described in the literature. The first was the Assessment of Discomfort in Advanced Alzheimer patients.[18] Since then, a number of instruments have been described, but none were well validated when reviewed in 2006.[19,20] A better validated brief instrument for measuring pain in non-verbal older people was published after these reviews.[21]

In parallel experimental studies of pain in demented patients, reflex behaviours have been observed to increase in situations of acute pain, such as venepuncture and mobilization, using measures of facial expression and nociceptive motor reflexes. Other studies have documented increases in brain activity of pain-associated areas of cerebral cortex in mildly demented subjects over cognitively normal control subjects. On the other hand, these same demented subjects consistently rate weak pain at threshold the same as cognitively intact controls, but pain tolerance is measurably higher with more advanced dementia from Alzheimer's disease, supporting the clinical contention that pain is under reported in this cohort.

The validity and reliability of these observations do not necessarily apply in situations of chronic pain. Nevertheless, with a similar history obtained from both family and professional carers, an examination demonstrating consistent evoked responses to movement of the affected body part and examination findings showing hypoalgesia or hyperalgesia, hyperpathia and allodynia, a picture consistent with nociceptive or neuropathic pain can be assembled. Other factors, such as hunger, constipation, urinary retention and urinary tract infection, must also be considered as causes of new onset abnormal 'pain' behaviours.

Following this assessment, patient discussion of potential treatments with family and carers is required and consensus on outcome measures for trials of treatment undertaken for predetermined periods of time determined. These treatments will include medications, physical therapies, environmental modification and limited exercise programmes, as is the case for cognitively intact individuals. The outcome measures include functional outcomes important for activities of daily living and also a selection from the pain measures described above. What has been learnt from experimental studies, however, is that placebo treatments are ineffective in patients with advanced dementia affecting the prefrontal cortex, such as with Alzheimer's disease, and they should not be used as treatments.

Management strategies

This section on pain management is of a general nature. Where specific conditions are mentioned, the purpose is to highlight a point rather than to provide comprehensive advice on how to manage that condition. For convenience, we have divided management strategies into individual modalities. The initial treatment modality is often determined by the type of health practitioner the patient has selected; whether medical, physical, psychological or complementary therapist. If initial strategies are not effective, then a multidisciplinary approach is recommended rather than simply escalating single-modality therapies. For patients presenting with troublesome persistent pain, a multifaceted management programme is frequently employed from the outset.[22]

Pharmacological management

Pharmacological management is the most common approach to the management of pain in older people. Here we focus on options that are readily accessible to medical practitioners. The American Geriatrics Society (2009) has published guidelines for the pharmacological management of persistent pain.[23] Practice guidelines on interventional approaches to management of chronic pain have been published by the American Society of Anesthesiologists and the American Society of Regional Anesthesia and Pain Medicine (2010).[24]

Although pharmacological management has become the mainstay of pain management in older people, it also carries a great risk of adverse outcomes. Therapeutic guidelines for older patients are often extrapolated from data available for younger patients and those with malignant pain. These data should be interpreted with caution. Published studies tend to be based on highly selected populations atypical of the patients seen on a day-to-day basis. Positive trial outcomes are often achieved over short time frames at doses much higher than those able to be tolerated by frail

older individuals. Age-related changes in drug handling and sensitivity are discussed in Chapters 12–14. As medical science is constantly evolving, any recommendations made here must be reconsidered by the reader as new evidence emerges.

The timing of analgesic medication and efforts to ensure compliance may be as important as the selection of the medication itself. Analgesia may be administered as pain-contingent (as required), time-contingent (at fixed time intervals) or prophylactic, that is, usually about 30 min prior to an activity known to exacerbate pain, such as with routine exercises or wound dressing changes. For persistent pain, analgesic medications should be given to provide 'round the clock' cover.

Adverse drug side effects are common and often predictable. Tolerance to side effects may be achieved by commencement at a low dose followed by slow upward titration. Explanation of benefits and disadvantages of treatments need to be openly discussed with patients and carers, particularly as the goal is to optimize pain relief and/or function without causing intolerable side effects. Attempts to eradicate pain entirely often result in unacceptable drug side effects. These may be as troublesome as the pain itself. Side effects can usually be managed effectively by dose adjustment or added medication that does not compromise analgesic benefits as, for example, with opioid-related constipation treated with laxatives. Where there is doubt, a short trial off the medication, or at a lower dose, may help determine whether, on balance, the medication is of benefit to the patient. For chronic pain management, the oral or transdermal route is preferred. Parenteral analgesics should be avoided.

Non-opioid analgesia

Paracetamol (acetaminophen) remains the first-line treatment for mild to moderate chronic pain. Its efficacy is not significantly different to that of ibuprofen. No age-related dose adjustment is required. In chronic pain it is usually prescribed in a dose of 1000 mg four times per day. Given the short duration of action and dose required to obtain maximum analgesic effect, some patients do better on a dose of 500 mg every 4 h. Long-acting oral preparations are available. They may be of benefit in reducing the number of doses per day and provide better overnight analgesic cover. The major concern with paracetamol toxicity is liver failure. The risk is enhanced by the large range of paracetamol-containing analgesics that are widely available without prescription. Different brand names may leave the patient unaware that they also contain paracetamol, resulting in inadvertently exceeding the maximum recommended daily dose. Although there is no entirely safe dose, paracetamol hepatic toxicity is rare in doses below 4000 mg per day. The risk is increased in alcoholics and malnourished individuals. A lower maximum dose of 3000 mg per day is recommended in this population.

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics and represent one of the most widely used classes of prescribed medication. Their use is limited by frequent adverse reactions in older people, including peptic ulceration and haemorrhage, drug interactions, renal impairment and fluid retention. The introduction of the selective cyclooxygenase-2 enzyme (COX-2) inhibitors was met with enthusiasm as a safer alternative to conventional NSAIDs in terms of upper gastrointestinal toxicity. There is, however, increasing concern about the safety of COX-2 inhibitors, particularly in older individuals. Rofecoxib was withdrawn because of serious thrombotic cardiovascular events in some patients taking this medication. There is no evidence that the increased cardiovascular complications observed with rofecoxib represent a class effect of the COX-2 inhibitors. COX-2 inhibitors appear to affect renal function in a similar fashion to non-selective NSAIDs. Particular caution is required in patients with renal impairment or when administered with diuretics and angiotensin-converting enzyme inhibitors. NSAIDs are best reserved for use in transient or subacute musculoskeletal pain which is thought to have an inflammatory pathogenesis, that is, nociceptive pain. They are of no benefit in neuropathic pain. The coadministration of a proton pump inhibitor with a conventional NSAID should be considered in high-risk patients. Prolonged use of NSAIDs beyond 2 weeks is best avoided.

Analgesics with weak opioid effects

For patients with pain not adequately controlled with simple non-opioid analgesia there is an intermediate step before embarking on treatment with strong opioids. The medications in this group include codeine, tramadol and dextropropoxyphene. As a group their efficacy is not always predictable and side effects are common.

Codeine (methylmorphine) is an opioid analgesic with a short half-life often given in fixed combination tablets with paracetamol, aspirin or ibuprofen. Recommended for incident, predictable, short-lasting and infrequent pain, its role in chronic pain management is less clearly defined. The smallest codeine tablet contains 8 mg. There is little evidence to support its efficacy at this dose. The analgesic effects of codeine require its transformation to morphine. About 8% of Caucasians and 2% of Asians have a congenital absence of the cytochrome CYP2D6 responsible for this conversion and therefore obtain little pain relief. Several medications may also interfere with this conversion, including the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine and the antihistamine dipheniramine. The maximum dose for older people is 60 mg four times per day, although many frailer individuals will only tolerate 30 mg four times per day. Codeine has a strong

tendency to cause constipation. Other common side effects include nausea and confusion.

Tramadol (hydrochloride) is an atypical, centrally acting analgesic with weak action on the mu-opioid receptor. It is usually classified separately from the opioid analgesics as it has additional pharmacological actions, inhibiting noradrenaline and serotonin reuptake. Short-acting preparations are often used for acute pain as they cause less respiratory depression and constipation than other opioids. Slow-release tramadol may be used for chronic pain, including neuropathic pain. For older patients, the maximum recommended dose of tramadol is reduced to 300 mg per day. Drug interactions and frequent side effects limit its use. Up to one-third of patients are unable to tolerate tramadol, experiencing symptoms such as nausea, vomiting, sweating, dizziness, tremors and headaches. Serious side effects include delirium and hallucinations. A serotonin syndrome can be precipitated when other serotonergic medications are used concurrently, including SSRIs and tricyclic antidepressants. Features of the serotonin syndrome include delirium, confusion, agitation, hypomania, hyperactivity, restlessness, fever, sweating, tachycardia, hypertension, ataxia and tremor. It may occur dramatically or insidiously. Mild forms usually resolve within 24 h of ceasing the medications.

Dextropropoxyphene is now used less frequently than in the past. If used, great caution should be taken in the elderly. Its major metabolite has a long half-life and has the potential for causing central nervous system side effects, including hallucinations and seizures. The usual dose is 32.5–65 mg four times per day.

The analgesic properties of codeine, tramadol and dextropropoxyphene are limited by a ceiling effect. Further dose increases may cause toxicity without conferring additional analgesia. It is our preference to use a low dose of a strong opioid rather than these agents if additional analgesia is required.

Strong opioid analgesia

Opioids have an established role in the treatment of severe malignant pain. Opioids are increasingly gaining acceptance for the management of severe non-malignant pain. This trend is seen as positive, in the sense that individuals should not be left to suffer uncontrolled pain. There is no optimal or correct opioid dose; the optimal dose is determined by a balance between analgesia and side effects. In some cases an increased dose does not result in increased analgesia. There is no evidence to support escalating opioid doses beyond the equivalent of morphine 180 mg per day if no response has occurred at lower doses. Clinicians must observe strict regulatory requirements when prescribing opioids. Prior to their introduction, the physician should engage the patient and carers in a discussion concerning these restrictions and why they are important to observe. Most older people are concerned about possible addiction and the discussion needs to include the distinction between habituation and addiction. It is best to introduce opioids on a trial basis with agreed objectives on functional goals, and if these are not achieved the medication should be withdrawn. It may be necessary to have these issues documented in a written agreement in some cases.

There is a paucity of evidence to support the long-term use of opioid medication for chronic non-cancer pain, especially among older patients. Ongoing monitoring is required to ensure that pain control has not occurred at the expense of intolerable side effects such as impaired cognition, falls or severe constipation. The clinician must evaluate the benefits and adverse effects for each individual patient. An exacerbation of previously controlled pain should not simply lead to dose escalation without assessment as to why the pain has become worse. It is possible to mask the symptoms of pathology where specific treatment is more appropriate.

All opioids have the tendency to produce constipation, nausea, sedation, cognitive impairment and respiratory depression, necessitating commencement at a low dose with gentle titration. There is significant individual variation in side effects with different opioids. Selection of the most suitable agent may require trials of a number of different agents. Tolerance to these side effects occurs over time, apart from constipation, which tends to persist. The onset of nausea several days or weeks after commencement of an opioid analgesic is more likely to be due to constipation than intolerance of the opioid. Prophylactic treatment of constipation is generally required. Aperients act as a source of increased fibre, are faecal softeners, osmotically active or act as bowel stimulants. Many aperients contain multiple active ingredients. It is best to gain experience with a few over-the-counter preparations before prescribing more expensive options. Enemas should be a last resort. A severely constipated patient with overflow incontinence may need inpatient monitoring of treatment with a preparation usually reserved for use prior to bowel investigative studies.

The most commonly prescribed oral opioids are morphine and oxycodone. Morphine has traditionally been considered the opioid of choice. Increasingly oxycodone is being used as the first-line opioid analgesic agent for older individuals. This is based on a more predictable dose–response relationship as it does not undergo extensive first-pass metabolism in the liver. Cognitive side effects are said to be less frequent.

Initiation of opioid analgesia for chronic non-malignant pain is usually commenced with oxycodone 5 mg or morphine 10 mg. The dose is titrated according to response. Once the maintenance dose has been determined, a long-acting oral preparation can be used. A short-acting preparation should also be prescribed for breakthrough

or incident pain. Breakthrough pain occurs unpredictably on a background of controlled pain, whereas incident pain is predictable, occurring for example with physical activity or wound dressings. Breakthrough pain is treated after the pain occurs, whereas incident pain should be managed prophylactically prior to the pain-inducing activity. A short-acting opioid is used, usually in the order of one-sixth to one-third of the daily maintenance dose.

A sustained analgesic effect is desirable for people with chronic pain. Various long-acting opioid preparations are available, including oral and transdermal preparations. These have the advantage of avoiding fluctuating blood levels and are less likely to be associated with mood-elevating effects seen with shorter acting preparations. Two long-acting transdermal opioid preparations are currently available with others under development. Transdermal opioid delivery systems are characterized by a delayed onset of initial action, making them unsuitable for the treatment of acute pain. A prolonged duration of action allows for less frequent dosing. Stabilization with oral therapy is recommended before transferring to a transdermal patch. The oral agent should be continued for a few days following initiation of the transdermal opioid-containing patch.

After application of the patch, the opioid accumulates to form a depot in the skin from where it gradually enters the circulation. Drug effects continue after removing the patch as the opioid is released from this depot. Transdermal therapy does not offer the range of dose flexibility of oral preparations. There is no efficacy advantage over oral opioids and their side effect profile is similar, although considerable individual variation in side effects exists. It is worth trying another agent if the first is not well tolerated. However, transdermal therapy increases the range of options, especially when oral therapy is associated with persistent nausea, vomiting, severe constipation or for patients with swallowing difficulties or compliance issues. Their long duration of action does have the advantage of ensuring 'round the clock' dosing. Patients should be warned of the dangers of exposing the patches to direct heat, for instance with a hot pack or electric blanket. There is a potential for temperature-dependent increases in opioid released from the transdermal systems, resulting in possible overdose and death.

Buprenorphine is a partial opioid agonist at mu receptors and an antagonist at kappa receptors. Buprenorphine transdermal patches are produced in two dose ranges. Availability varies between countries. The lower dose range transdermal patches, releasing 5, 10 or 20 μg of buprenorphine per hour, is indicated for non-malignant pain not responding to non-opioid analgesia. They require changing every 7 days. The lowest dose buprenorphine transdermal patches may be used to initiate strong opioid therapy. The 20 μg per hour buprenorphine patch is approximately equivalent to a fentanyl 12 μg per hour patch. Higher dose transdermal patches releasing 35, 52.5 or 70 μg of buprenorphine per hour are indicated for moderate to severe cancer pain not responding to non-opioid analgesics. They require changing every 4 days.

Fentanyl is available in different forms, including a transdermal patch that is replaced every 3 days. Even the lowest dose fentanyl patch is too potent for patients who are not already on opioid therapy. The fentanyl 12 μg per hour patch equates to oral morphine ~45 mg per day. Older, cachectic or debilitated patients may be more sensitive to fentanyl because of reduced clearance and a prolonged half-life. As fentanyl is primarily metabolized in the liver, it has a role in patients with severe renal impairment. The used patches retain a significant quantity of residual fentanyl and must be disposed of appropriately. After patch removal, fentanyl concentrations fall slowly, decreasing by 50% after 17 h.

Methadone has a long and unpredictable half-life, making it difficult to prescribe. There is a potential for it to accumulate, resulting in agitation, tremor or seizures. In general, we recommend that methadone be reserved for use by clinicians experienced with its use, such as pain and palliative care specialists. Methadone may have a special role in settings with limited access to the more expensive long-acting opioid preparations. The use of pethidine (meperidine) for chronic pain is not recommended because of the potential for neurotoxicity associated with the accumulation of the metabolite norpethidine.

It has been shown that only approximately one-third of patients with chronic pain respond well to opioid analgesia, one-third respond partially and one-third do not respond.[25] Of the responders, only half continued to benefit in the long term. This compares poorly with their use in malignant pain, where 90% of patients will have opioid responsive pain. The risk–benefit ratio in older patients is currently unknown. In general, older patients respond to lower doses of opioids where fewer side effects are expected, but have a greater tendency for adverse effects. Opioids are not a panacea for chronic pain and are best employed as part of a multifaceted pain management programme.

Adjuvant analgesics

Neuropathic pain can be difficult to treat as conventional analgesics often fail to provide effective pain relief. Most therapeutic trials are based on a 50% reduction in the level of pain being considered an appropriate endpoint. Total eradication of pain is rarely achieved, the dose being limited by drug side effects. Although only partially effective, however, pharmacological therapy remains an important intervention. As less than 50% of patients will get adequate pain relief with a single drug, neuropathic pain is usually treated with a combination of conventional analgesics

and adjuvant agents. Adjuvant agents are not primarily analgesics, although they have been shown to be of benefit in the management of neuropathic pain. They comprise drugs from a number of different therapeutic classes including antidepressants, antiepileptic drugs, antiarrhythmics and *N*-methyl-D-aspartate receptor antagonists (NMDA antagonists).

Consensus guidelines are available to assist the clinician with the selection of therapeutic agents.[26] These must be interpreted with caution. The evidence is often based on short-term trials of 6–12 weeks' duration, often with very few older people being included and without evidence for long-term use spanning many years, as is often the case when they are used clinically. There have been few studies directly comparing the efficacy of the different agents or combination of agents. The trials tended to focus on common neuropathic conditions such as painful diabetic peripheral neuropathy and post-herpetic neuralgia, offering little guidance to other conditions such as pain arising from radiculopathy, surgery, spinal cord lesions or post-stroke central pain syndromes.

The most commonly used agents for neuropathic pain include antidepressants and antiepileptic drugs. Many of the earliest studies were undertaken with the tricyclic antidepressants amitriptyline and nortriptyline. Great caution should be used with these medications in older patients. The presence of depression is not required for the analgesic effects. They are inexpensive and usually administered once daily. Based on their efficacy in these relatively inadequate trials, they remain in the list of first-line agents for neuropathic pain, joined in recent times by newer agents with better side effect profiles, especially in older people. However, tricyclic antidepressants continue to have a role when access to the newer, more expensive alternatives is not available. Amitriptyline and nortriptyline are usually commenced at 10 mg 1 h before retiring and increased every few days by a similar dose until a benefit is achieved or side effects preclude further use. A dose of 50 mg is usually considered to be sufficient to achieve an analgesic effect if one is going to occur. Common side effects include dry mouth, postural hypotension, drowsiness and urinary retention.

Because of more favourable side effect profiles, SSRIs and selective serotonin and noradrenalin reuptake inhibitors (SNRIs) have largely replaced the tricyclic antidepressants for the treatment of depression. SSRIs have not been shown to be effective for neuropathic pain. The SNRIs duloxetine and venlafaxine have, however, been shown to be effective in neuropathic pain states such as diabetic peripheral neuropathy. In low doses venlafaxine only inhibits serotonin reuptake, but in higher doses it inhibits both serotonin and noradrenaline reuptake. Hence the analgesic effects of venlafaxine may not become apparent until higher doses are reached or a concurrent low dose of a noradrenaline reuptake inhibitor is added. Care should be taken with both dose escalation and dose reduction with these agents. They are contraindicated if monoamine oxidase inhibitors (MAOIs) are in use. Many precautions, adverse events and other drug interactions have been linked to these drugs. They should only be prescribed by practitioners familiar with their use.

Gabapentin and pregabalin bind to the alpha 2-delta subunit of voltage-gated calcium channels, decreasing the release of glutamate, adrenaline and substance P near primary afferent nerve terminals in the spinal cord. They have been proven to be of benefit in a number of painful neuropathic conditions, including post-herpetic neuralgia, painful diabetic peripheral neuropathy and spinal cord injury. The main dose-limiting side effects are somnolence, dizziness and unexplained peripheral oedema.

In some patients, particularly older people, gabapentin can cause or exacerbate cognitive or gait impairment. The usual starting dose of gabapentin in the frail elderly is 100 mg at night, increasing every few days, aiming for 300 mg three times per day. This is below the target therapeutic dose in most trials of 1800–3600 mg per day, but these doses are generally not tolerated by frail older patients.

Pregabalin has similar side effects to gabapentin but is easier to titrate and has no important drug interactions. The usual starting dose in the elderly is 75 mg at bedtime, titrating upwards to 150 or 300 mg daily, in divided doses. Dose reduction is required for both gabapentin and pregabalin in renal impairment and 25 mg capsules of pregabalin have recently become available.

Carbamazepine is the drug of choice for trigeminal neuralgia. A starting dose of 50 mg is suggested, as some older people are very sensitive to the adverse effects of this medication.

Lignocaine (lidocaine) 5% patches are effective for the management of post-herpetic neuralgia with allodynia and painful diabetic peripheral neuropathy. Blood levels are minimal with standard doses; the most common side effects are mild skin reactions. Cost may preclude its use. Lignocaine 5% gel may be considered as an alternative. Oral local anaesthetic preparations such as mexiletine have low therapeutic benefit to toxic ratios and are generally precluded from use in older people.

NMDA antagonists such as ketamine should be reserved for use by clinicians experienced with its use as side effects are common and often severe. The use of clonidine for prevention of withdrawal symptoms due to reductions in opioid doses is to be avoided in older people.

Complementary therapies

Complementary therapies comprise a group of healthcare practices and products that are not considered to be conventional medicine. These include herbs, acupuncture, mind–body techniques, massage and chiropractice.

The use of complementary therapies is increasing, perhaps because of personal beliefs or disillusionment with conventional medicine due to lack of efficacy or side-effects. Complementary therapies are generally safe when provided by a competent practitioner. Herbal therapies are biologically active, raising concern about potential interactions with conventional therapy. For example, St John's wort (*Hypericum perforatum*) when used in combination with other antidepressants may induce a serotonin syndrome as it is a weak MAOI. It may also interfere with anticoagulation when coadministered with warfarin. Many patients do not disclose their current use of complementary therapies and they are often not specifically asked by their physicians.

Glucosamine is widely used for osteoarthritis, often in combination with chondroitin sulfate. A Cochrane review of glucosamine for osteoarthritis reported significant advantage for pain and function over placebo, but no benefit when analysis was confined to the higher quality studies with adequate allocation concealment. There was also variation between product manufacturer and benefit. Most study populations were of people in their 50s and 60s. Although the efficacy of glucosamine is questionable, it is generally safe.[27]

Acupuncture has been demonstrated to be a safe therapy with a very low risk of serious side effects. A Cochrane review of acupuncture for knee and hip pain reported a small improvement with acupuncture compared with sham acupuncture. The effects of acupuncture relative to sham acupuncture are too small to be perceived by participants as beneficial. These benefits may be largely mediated through placebo effects.[28]

Other pharmacological measures

Depression and anxiety are common accompaniments of chronic pain. Many patients receive pharmacological therapies to relieve these symptoms. However, they are best used in the context of a multidisciplinary management programme rather than as a sole modality of treatment, unless the disorder is primarily affective in nature. Benzodiazepines do not have a direct analgesic effect. The high potential for adverse effects in older patients limits their usefulness for insomnia or anxiety associated with chronic pain. Corticosteroids play a valuable role in the management of a number of painful conditions, including polymyalgia rheumatica, temporal arteritis, rheumatoid arthritis and crystal arthropathies. Serious adverse effects limit their long-term use. Topical agents are also widely used by older people. The most common are those containing capsaicin, NSAIDs, local anaesthetics and the rubifacients methyl salicylate and nicotinate. Although of limited efficacy, they are relatively free of systemic side effects.

Psychological modalities of management

Most multidisciplinary chronic pain management programmes are based on the cognitive behavioural therapy (CBT) model. Such programmes consist of patient and family education, contingency management, relaxation training, training in goal setting and problem-solving skills, training in effective communication, behavioural reactivation and cognitive restructuring. The last requires attention to specific constructs identified in individual patients. These might include a fear of increased damage from activity or increased pain levels or excessive reliance on 'powerful others' such as doctors and medications. The efficacy of CBT in the general population has been shown to have unequivocal benefit. However, there have been limited studies in older people. It has been shown that 10 weekly sessions of CBT are effective in the institutionalized elderly[29] and that age is not a factor in determining the success of a CBT programme.[30] CBT is also useful in the treatment of depression in older people. CBT programmes should be undertaken under the supervision of a psychologist experienced in their use.

Physical modalities of management

Exercise therapy has been used as a part of CBT programmes. It is most effective if it has a specific goal orientation. Exercise therapy should include stretching, strengthening, aerobic exercise and postural correction where feasible. Weight loss can help in painful conditions involving the weight-bearing joints and can assist in slowing the progression of degenerative arthritis. Other techniques, such as bracing, trigger point deactivation, massage therapy, acupuncture, transcutaneous electrical stimulation (TENS), heat and cold, have also been used. Hydrotherapy and use of an exercise bike may promote increased range of movement and confidence. TENS is useful in subacute injury and post-herpetic neuralgia. Controlled trials of TENS using experimental pain models are usually only effective at high intensities of stimulation. TENS has the advantage of being able to be used for long periods at a time, but post-stimulus effects are short-lived.

The clinician should be aware of the dangers of an over-reliance on passive therapies, especially if the patient tends to have an external locus of control. Advice on simple manoeuvres for lifting and walking may be of great functional benefit; for instance, leaning on the supermarket trolley in patients with vertebral canal stenosis may increase their walking distance. The use of assistive devices, such as walking sticks and wheeled frames, can be useful in patients to improve function and reduce pain. However, such measures should be applied judiciously so as not to promote over-reliance on them or promote deconditioning. Physiotherapists can also counsel patients in approaches that avoid exacerbations of musculoskeletal pains.

Management of social circumstances

The patient's family must be educated about the nature of chronic pain. First, they must be assured that the problem is real and the patient is not in any way trying to 'fake the pain' to obtain some advantage. Second, they must be educated that although the aim is to decrease pain and maintain function, the patient may be better satisfied with the same pain but better function. The nature of how solicitous behaviour can modify the patient's function should be explained to carers. The family should also be educated about the need to maintain a paced level of physical activity and be taught the same methods of non-pharmacological pain management as the patient. Such measures may increase the sense of mastery of both patient and family. The family may play an important role in the management of patients with dementia, who may not be able to maintain a therapeutic approach without ongoing prompting and supervision. Frequently, loneliness and meaninglessness can present as somatic complaints, including pain. Pain management in these instances may be helping the patient source social or meaningful activities.

Procedural modalities of management

Ongoing pain may warrant consideration of anaesthetic or surgical interventions. Joint arthroplasty of the hip and knee is a good example of interventions that improve pain and function in appropriately selected older individuals. The place of vertebroplasty in vertebral collapse is not yet fully established. Other interventions such as CT controlled epidural injections of local anaesthetics and steroids may give short-term relief, especially into nerve root sleeves of patients with painful radiculopathies not settling with more conservative treatments. Most studies of anaesthetic interventions have not included older subjects, in particular those in residential care. Assessment needs to be undertaken on an individual basis. Referral to a multidisciplinary pain clinic or pain specialist should be considered when planning procedures in frail patients.

Key points

- Chronic pain is a common complaint among older people.
- Older people have higher pain thresholds and lower pain tolerance than young adults in studies of experimental pain. This is probably also true in chronic pain syndromes.
- Chronic pain requires meticulous multidimensional assessment and properly planned and monitored interventions using pharmacological, physical, social and psychological modalities.
- Chronic pain is best managed with a combination of pharmacological and non-pharmacological approaches.
- Empowerment is a key factor in ensuring satisfying and durable outcomes; the patient and their carers must be active participants in therapy at all times.
- Although there is limited high-quality information about the management of chronic pain affecting older people, this is likely to be rectified in coming years as chronic pain is increasingly recognized as an important geriatric syndrome.

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CHAPTER 70

Multiple sclerosis

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Introduction

As individuals with multiple sclerosis (MS) grow older, not only does this condition typically lead to more disability,[1] but often they acquire additional unrelated medical problems such as diabetes, hypertension, hyperlipidaemia, cardiac and peripheral vascular diseases, osteoporosis and dementia. Consequences of MS accumulate, including paresis, neurogenic bowel and bladder, depression, cognitive decline, fatigue, gait imbalance and pain. Engagement in appropriate health behaviour is often limited. The death of a spouse may contribute to social withdrawal and loss of cognitive stimulation. Thus, advanced MS in an ageing individual may present formidable challenges, and treating one problem may make others worse. These numerous medical issues are often beyond the scope of a single healthcare provider, whatever the specialty. A person with MS, faced with advancing age and disability, may be obliged to engage multiple providers who schedule numerous appointments. Accessing these appointments may become near impossible owing to loss of the ability to drive, inadequate accessibility of public transportation and doctors' offices and lack of social networks necessary for assistance. Persons with MS may live without significant others or relatives who could provide logistical, emotional and social support. They may lack the resources to hire personal assistants or their significant others may also have medical problems that render them incapable of helping. Deterioration, depression and social isolation may be inexorable. Nursing homes rarely provide optimal care, but may prove the only viable, albeit unsatisfactory, alternative.

This picture is reality for many patients. Some have a more benign course, with minimal disability decades after the diagnosis and few comorbidities.[2] However, for the majority a comprehensive paradigm that engages persons with MS and their network in the healthcare process is required. This approach does not gloss over clinical features such as fatigue but addresses all manifestations of MS and comorbidities in an all-encompassing fashion. It seeks to integrate numerous providers in ongoing multilateral communication. Such a team will likely include internists, neurologists, nurses, psychiatrists, psychologists, rehabilitation therapists, social workers and urologists, among others. It optimizes access to insurance-covered home care and utilizes other community resources, for example, from the National MS Society, independent living centres or other organizations. Such an approach can significantly enhance quality of life.

The impact of disease-modifying drugs such as glatiramer acetate and beta-interferons on the gestalt of the ageing person with MS is only beginning to be felt. Such agents reached the market starting in 1993. People who turn 60 years of age in 2011 were in their early 40s when they would have received their first dose. Thus they could have lived with MS for up to 20 years before benefiting from these drugs.[3,4]

Although there is no cure for MS, the advent of these drugs fostered optimism among patients and healthcare providers that devoting time and energy in clinical practice, in clinical trials and the laboratory ameliorates outcomes. Although, as will be discussed here, access to optimal care remains limited for many affected individuals, multidisciplinary MS centres have been established in larger towns and cities, where the many needs of patients are being recognized and met.

This chapter discusses the major clinical entities and ancillary studies that must be considered in the care of persons with MS and focus on the health of individuals with MS as they age. It assumes that the disease onset is not recent and that the diagnosis is valid and confirmed. For a comprehensive discussion of the aetiology, pathogenesis, pathology, clinical presentation, ancillary studies and use of disease- and symptom-modifying drugs, the reader is referred to standard texts.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Pathophysiology, aetiology and epidemiology

With a putative overall prevalence of 1 in 1000, some 2.5 million persons worldwide are affected by MS, about 400 000 in the USA, with 10 000 new diagnoses each year.[5] The prevalence varies considerably with distance from the equator and between different countries and ethnic origins.

MS has been defined as an autoimmune disease in which inflammation is sustained by autoreactive T cells directed against components of myelin.[6] A broader concept accounts for the influence of B lymphocytes, for modulation by cytokines and their receptors, for an aetiological role of a primary oligodendropathy and the notion that not only clinically different, but even clinically identical, forms of MS may result from different pathomechanisms.[7] Cytokines not only function as immune modulators but also impact clinical features, including fatigue and cognition. Inflammatory cells including macrophages and lymphocytes cross the blood–brain barrier to enter the central nervous system (CNS). There, in cooperation with cytokines and antibodies, they recognize myelin and axonal antigenic targets and damage them functionally and structurally, thus causing slowing of nerve conduction, demyelination and axonal loss in the white and grey matter, which presents as clinical attacks with varying and multiple symptoms and signs. During remission, inflammatory oedema diminishes and demyelinated axons are repaired. However, irreversible destruction of axons starts soon after onset and contributes to incomplete recovery from attacks and disease progression.

Numerous microbial antigens have been implicated as inducers of autoimmunity, including viruses which may damage oligodendrocytes, such as Epstein–Barr virus (EBV).[8,9] Recently infection with the herpes zoster virus has been established as a risk factor.[9a] Sunlight exposure, vitamin D levels and tobacco use are independent risk factors, among others.[10,11] Evolving concepts include the notion of chronic cerebrospinal venous insufficiency.[12] Beyond the role of autoimmunity, MS likely reflects complex polygenetic–environmental interactions. The risk in families increases with relatedness.[13] The prevalence is related to increasing distance from the equator. The risk conveyed by ethnic origin is modified by geographic origin.

Clinical spectrum, diagnosis and treatment

As MS lesions can affect any anatomical region in the CNS, clinical features may reflect involvement of sensory and motor systems in the brain or spinal cord and of motor, sensory, visual, cerebellar, brainstem, bladder, bowel, sexual, cognitive and emotional functions. Fatigue, sleep disturbances and hormonal anomalies are common but underdiagnosed.

Taking a history may require repeated follow-up questions because the language that patients choose is often idiosyncratic. Open-ended questions yield more valid information. It is helpful to point out the distinction of positive (cramps, spasticity, tingling, vertigo) versus negative symptoms (weakness, numbness, imbalance), both in order to ensure that what the patient tries to convey and what the provider documents as a symptom are not at odds and in order to facilitate rational treatment and realistic expectations of the likelihood of success. For instance, some people use the word numbness to describe tingling or mild weakness rather than sensory loss; some experience tingling as painful, others as a nuisance. Although positive and negative symptoms often go hand in hand, patients should be aware that a medication can alleviate tingling but not numbness.

The diagnosis of relapsing MS requires that a person display dissemination in time and space, for example, optic neuritis and vertigo 3 months apart, for which no better alternative explanation is apparent, such as two separate cerebrovascular accidents affecting different CNS regions in an elderly smoker with hypertension, diabetes and hyperlipidaemia.[14] The accumulation of comorbidities with age (see below) may render a new diagnosis of MS and also the interpretation of new symptoms and signs in the case of an established diagnosis more difficult. Also, when primary progressive MS is entertained, it is important also to consider cervical myelopathy and primary lateral sclerosis, to give just two examples.[14]

Ancillary studies

Imaging studies such as magnetic resonance imaging (MRI) serve different purposes at different disease stages.[15] At onset, MRI can confirm the diagnosis and rule out other conditions. MS-like MRI lesions occur in many other conditions, including vascular disease, migraine and vitamin B_{12} deficiency. MRI can relate the clinical presentation to plaque location and quantitate disease activity, thus providing evidence of therapeutic efficacy. As a person with MS ages and clinical manifestations evolve, CNS imaging can evaluate for intercurrent illnesses such as subdural haematoma (e.g. after a fall), stroke, dementia or mass lesions. Plaques are often ovoid, concentrate in the corpus callosum and periventricular white matter and extend peripherally. New plaques show T2 hyperintensity and enhance with gadolinium. Later they no longer enhance, but maintain T2 hyperintensity and may become T1 hypointense, the so-called black holes which indicate axonal loss, gliosis and demyelination. White matter lesions are easier to detect than those in the grey matter. Brain atrophy starts shortly after onset, results from demyelination

and axonal loss and is accelerated in progressive MS, but slowed by disease-modifying drugs. Serial MRIs reveal a ratio of subclinical to clinical lesions of 5:1. The relationship between brain volume, clinical and MRI exacerbations and disability is beyond the scope of this chapter. Impaired renal function is a risk factor for gadolinium contrast-associated nephrogenic system fibrosis. When contrast is required, its dose should be minimized and alternative contrast agents considered.

Cerebrospinal fluid (CSF) analysis reveals CNS inflammation and may show lymphocytic pleocytosis, protein elevation and evidence of abnormal CNS immunoglobulins.[16]

Evoked potential studies (EP) are abnormal in 70% (somatosensory EP), 90% (visual EP) and 80% (brainstem auditory EP) and can serve to provide evidence for subclinical involvement of functional pathways, in particular when MRI is normal.[17]

Certain blood tests can confirm that no other more appropriate or concurrent diagnosis is warranted, including erythrocyte sedimentation rate, C-reactive protein, rheumatological assays, vitamins B_{12} and D, folate, thyroid function, infections such as syphilis, Lyme disease and hepatitis, HgA1c and urine analysis and culture.

Clinical subtypes

Multiple forms of demyelinating inflammatory CNS disease can be distinguished which differ in pathogenesis, clinical manifestations and treatment options.[18]

At onset, 85% of individuals have relapsing–remitting MS (RRMS), with attacks about every 2 years, characterized by a fairly well-defined deterioration in neurological status followed by variable recovery. Two to three times as many women as men are affected. The typical age at diagnosis is 20–50 years. MS attacks typically evolve from first symptom to maximum deficit over 1 day to 1 week, although onset may be faster or slower. Remission from maximum deficit to maximum improvement usually occurs over 1–3 months, but again may be slower or faster. Some symptoms and signs are more likely to improve than others: Sensory symptoms remit completely in >75% of cases. Monoparesis or hemiparesis remits completely in 50%, but fewer than 20% of patients with tetraparesis or paraparesis recover to normality. With sphincter symptoms, only 15% regain complete control. Resolved symptoms can manifest again with intercurrent illnesses or heat exposure (Uthoff phenomenon). About 50% of patients after 10 years and about 90% after 25 years no longer experience relapses and remissions but progressively accumulate disability: they have developed secondary progressive MS (SPMS), because cumulative and ongoing CNS damage has surpassed a critical threshold, for example, the oligodendrocyte progenitor pool and intact tissue can no longer compensate. In progressive relapsing MS (PRMS), relapses are superimposed on a chronic progressive course already at onset.

FDA-approved subcutaneous or intramuscular beta-interferons[3] and subcutaneous glatiramer acetate[4] reduce the frequency of MS attacks and of disease activity and slow disease progression and brain atrophy. In cases of disabling MS attacks, intravenous or oral methylprednisolone is indicated to hasten recovery. FDA-approved mitoxantrone and natalizumab may be used to 'rescue' patients non-responsive to more benign drugs. Potentially life-threatening side effects, including acute myelogenous leukaemia and cardiotoxicity, and opportunistic infections, respectively, must be balanced against their efficacy. Other chemotherapeutic agents such as cyclophosphamide, methotrexate, mycophenolate mofetil and azathioprine, although not FDA approved, can also be considered for selected patients.

Primary progressive MS (PPMS) accounts for 10–15% of patients: relapses and remissions do not occur. Spinal cord features predominate clinically and by MRI. Onset is later and men and women are equally affected. The distinction of PPMS and SPMS is important because no drugs have been found effective in PPMS, but challenging because 28% of individuals with a progressive course eventually experience relapses.[19] Other subtypes refer to disease stage such as clinically isolated syndrome (CIS) and specific presentation and pathomechanisms such as neuromyelitis optica (Devic syndrome, NMO) and transverse myelitis (TM). The severity and completeness of spinal cord involvement in TM and NMO typically are more dramatic than in classical MS.

Patients with so-called 'benign' MS and little disability decades after the diagnosis typically have a monosymptomatic course without spinal cord features, rare exacerbations, onset at a young age and few lesions by MRI. However, these characteristics do not allow a prediction of such a course in a given individual and a decision against disease-modifying drugs must be individualized.[20]

Visual, brainstem and cerebellar dysfunction

The optic nerves are affected in over 60% of patients. Optic neuritis is a common presenting feature. As new onset optic neuritis is not common in older adults, readers are referred to standard texts for a detailed discussion. Symptoms include blurring of variable severity, scotomata, impaired colour perception and eye pain worse with eye movement.

Common cerebellar manifestations include nystagmus, scanning dysarthria, intention tremor of the limbs, ataxia, dysarthria and titubation. Dysarthria can also result from cerebral and brainstem lesions. Severe tremor can be extremely disabling and is very difficult to treat pharmacologically. Counterweights attached to the arm can reduce its amplitude and facilitate activities of daily

living such as eating. Ataxia is amenable to physical (PT) and occupational therapy (OT).

Brainstem lesions can cause neurological manifestations by disrupting motor, sensory and autonomic fibre tracts, the nuclei and intra-axial fibres of cranial nerves and connecting fibres between nuclei. Eye movement abnormalities including nystagmus, internuclear ophthalmoplegia and diplopia result from lesions that affect the third, fourth and sixth cranial nerves, their nuclei and connecting fibres. Even subtle manifestations such as impaired pursuit and nystagmus can interfere with reading and driving and must be differentiated from decreased visual acuity. The seventh cranial nerve and nucleus involvement resembles Bell palsy, but may be bilateral. Owing to its proximity, the sixth cranial nerve is often affected simultaneously. Vertigo is common in MS and with ageing in general and can be very disabling. Modestly effective drugs such as meclizine can compromise alertness and cognition. When there is a positional component, the Epley particle repositioning manoeuvre should be considered.

Sensory manifestations

Sensory loss can involve any of the senses and be spotty, radicular, reflect a spinal cord level or involve parts of a limb or an entire limb. Symptoms may resolve as patients recover from an attack or they can persist. Propriceptive and vibratory loss and other modalities are often dissociated. In addition to dysesthesias such as tingling, pins and needles, burning (and countless other descriptors), some patients describe a sensation of tightness around the chest or abdomen due to a spinal cord plaque.

Pain

Pain affects about 50% of people with MS and is severe in about 25%. Its causes and features are numerous: pain can originate in the optic nerve, brain or spinal cord, including root entry zones, and may be tingling, boring, aching, excruciating, episodic or chronic, radiculopathic and debilitating (e.g. tic douloureux). Spasms can affect limb muscles and the bladder. Constipation can cause visceral pain. Often several types of pain coexist. Disability can lead to a sedentary lifestyle and weight gain, which together with poor posture and degenerative joint disease can contribute to musculoskeletal back and joint pain. Headaches are more common in MS than the general population. Interferons occasionally cause vascular headaches, hence a pre-existing history of migraine must be considered when choosing a disease-modifying drug.

Treatment is challenging, in part because medications can exacerbate clinical features such as fatigue, memory and sphincter problems, in part because their benefit is often limited and they may be habit forming. Discussions with patients should address the difference between 'healing' and 'curing'. 'Healing' is a multidimensional path toward wellness, which allows individuals to explore opportunities for mental, emotional and spiritual balancing despite chronic illnesses. 'Curing', by contrast, with its focus on symptom eradication, is often unrealistic in the case of chronic illnesses.

Treatment success is more likely if a multidisciplinary team that includes a psychologist, a pain physician and a rehabilitation therapist works with a patient. A patient-oriented exploration of the gate control theory of pain[21] can serve as a springboard for pain management. In the context of mind–body strategies, patients learn that the pain experience is influenced by emotional (e.g. depression), mental (e.g. catastrophizing) and physical (e.g. type of injury) factors and that it can increase one's perception of stress, which in turn can make pain worse through increased muscle tension and anxiety. Issues that must be addressed include catastrophic thinking which manifests as a sense of helplessness and inability to shift one's focus away from pain and fear and avoidance of activity. Two strategies that can reduce pain and stress focus on relaxation and mindfulness.[22]

Although a full discussion is beyond the scope of this chapter, medication management begins with an analysis of the causes of the pain syndromes and associated conditions. The armamentarium includes muscle relaxants and drugs otherwise used to treat seizure or mood disorders,[23] but also acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) for musculoskeletal pain. CNS polypharmacy and drug dosing must be kept at a minimal effective level, because many pain medications exacerbate fatigue and cognitive, sexual and neurogenic bowel and bladder dysfunction. It is the sum total of CNS active medications that determine side effects, not just the most recent addition. Although, for instance, agents such as nortriptyline and topiramate are useful, they can also lead to or worsen cognitive impairment and fatigue, especially if a patient already takes anticholinergics for bladder problems or muscle relaxants. Some medications can be associated with weight gain (e.g. tricyclics), others with weight loss (e.g. topiramate). Opioids should be considered in severe chronic pain and be used in conjunction with an opioid treatment agreement and random urine drug screening. Long-acting opioids may be preferable. For refractory pain, intrathecal drug administration is an option.

Muscle weakness and other motor manifestations

Any muscle group can be affected, but the legs are typically more involved than the arms, likely because of the longer course of the corresponding corticospinal fibres. Patients may have weakness limited to part of limb, e.g. foot drop,

or an entire limb, or have hemiplegia, paraplegia or tetraplegia. While spasticity, spasms, extensor plantar responses, hyperreflexia and reflex spread are common, hyporeflexia can result from intra-axial spinal root involvement and complete spinal cord lesions. Baseline spasticity and spasms can transiently worsen after interferon injection and with many intercurrent infections, bladder or bowel distension, pressure ulcers, deep vein thrombosis and fractures which may go unrecognized in the face of severe sensory loss, osteoporosis and minimal trauma. Spasms and spasticity can result in intense and frequent pain and also fatigue.

PT, OT and exercise have multiple benefits. They can reverse deconditioning, reduce fatigue, spasms and spasticity, improve strength, enhance social interactions and emotional wellbeing, benefit constipation and facilitate weight control. Weight-bearing exercise may reduce osteoporosis. Overexertion must be avoided. Weight loss itself can reduce pain and increase endurance. Crutches and bracing may improve function. Weakness can respond to cooling such as with cooling vests and AC adjustments. Swimming may allow for exercise that avoids body temperature increases.

Drugs such as baclofen, tizanadine and diazepam improve spasticity and spasms, but can cause lethargy and weakness, in particular at higher doses. Withdrawal from such drugs can cause confusion and seizures. It may ensue when a provider is not aware of a patient's prescription or does not know that such medications should not be stopped abruptly. Botulinum toxin may be helpful when spasms and spasticity are restricted. In refractory spasticity/spasms, intrathecal baclofen is often helpful, as high spinal levels are achievable without compromising cognition.

Periodic leg movement and restless leg syndrome, while common in MS, warrant consideration of intercurrent conditions such as peripheral neuropathy and metabolic disturbances. Dopamine agonists, benzodiazepines and opioids can be beneficial.

Gait and coordination disorders

Some of the most challenging manifestations of MS are tremor and ataxia. Gait disorders are often complex and reflect the sum total of abnormalities in several functional systems, such as apraxia, ataxia, weakness, proprioceptive dysfunction, vertigo and visual impairment. Ageing compounds these issues. Abnormal posture and gait may damage joints. The risk of falls and near falls is high. A fall frequency of one per week is common and with a high prevalence of osteoporosis due to female preponderance, steroid use, sedentary lifestyle and likely hypothalamic dysfunction, fractures are a common result. Thus imbalance must further intensify the focus on primary and secondary prevention of osteoporosis and vitamin D deficiency. Community ambulation is compromised before household ambulation. Gait disorders can be amenable to rehabilitation, particularly in the context of a specialized balance clinic. Many patients avoid assistive aids or use inappropriate simple canes, for fear of the stigma associated with them. Often the benefits of quad canes, walkers and wheeled walkers must be repeatedly pointed out. Dalfampridine is an FDA-approved aminopyridine derivative that improves walking speed in persons with MS. At some point, a referral to a wheelchair and seat cushion specialist may be indicated. Assistive devices must be continuously adjusted for ongoing changes, including disability, skin breakdown, weight, hand function, development of entrapment neuropathies resulting from compression and repetitive movement (due to wheelchair use) at the wrist and elbow, cognitive function and many others.

Arm weights and bracing can reduce the amplitude of tremors. Many drugs have anecdotal efficacy, including baclofen, clonazepam, gabapentin, levatiracetam, primidone, propranolol, topiramate and odansetron. Deep brain stimulation or radiosurgery may be considered.

Fatigue and sleep disorders

Generalized physical and mental fatigue affects about two-thirds of people with MS.[9] Fatigue is one of the most common and often undertreated features of MS. It jeopardizes a person's quality of life and ability to work and participate in family life. It can be unprovoked or result from exertion. MS attacks presenting as monosymptomatic fatigue present diagnostic challenges. Fatigue is worse in the afternoon, during the luteal phase of the menstrual cycle and with high ambient temperatures (Uthoff phenomenon), all of which slightly raise body temperature and thus impair impulse conduction in demyelinated axons. Magnetic resonance spectroscopy and positron emission tomography may show frontal lobe abnormalities. Fatigue is distinct from tiredness, sleep deprivation, depression, deconditioning and weakness, any of which, however, may be comorbidities. Medications, hypothyroidism, anaemia and many other medical conditions must be considered as causes, but may also be cofactors of fatigue.

Once intercurrent illnesses and precipitating factors have been addressed and patients have been educated about energy-conserving and fatigue-avoiding techniques such as moving strenuous activities to the cooler times of the day, using cooling vests or hats and drinking cold liquids, medications such as amantadine, modafinil and methylphenidate should be tried. Fatigue may also improve with the institution of disease-modifying drugs and antidepressants.

Sleep disorders in multiple sclerosis are heterogeneous and often profound. Insomnia and fatigue/tiredness often coexist. Sleep studies may reveal restless leg syndrome, periodic limb movements, circadian rhythm disruption and hypersomnolence. As disordered sleep in general and sleep

apnea are associated with daytime tiredness, poor daytime function, cognitive impairment, depression and many other medical complications, their diagnosis and treatment are crucial. However, continuous and bi-level positive airway pressure (CPAP and BiPAP) treatment has one of the lowest adherence rates of any medical intervention and therefore requires close follow-up to optimize individualized settings and maximize comfort. This is particularly true given that sleep in people with advanced MS is often compromised in all stages by pain, impaired bed mobility and the need for trips to the bathroom due to neurogenic bladder symptoms.

Neurogenic bowel

About half of MS patients suffer gastrointestinal symptoms, typically constipation. Rare incontinence results from unawareness of rectal filling. Symptoms are associated with impaired voluntary squeeze pressure and rectal sensation by rectal manometry. Cord involvement is common and may indicate affection of sympathetic and parasympathetic pathways. Colonic transit time may be slowed because of autonomic involvement or physical inactivity. Cofactors, partially amenable to intervention, include a sedentary lifestyle due to physical disability, fatigue, depression, poor nutrition and CNS polypharmacy with anticholinergics, antidepressants and muscle relaxants. Lack of thirst and voluntary reduction of fluid intake for fear of urinary incontinence can contribute. The judicious use of stool softeners, stimulants and bulk forming agents including bisacodyl and docusate enemas, may provide relief. With complete spinal cord dysfunction a bowel programme is often indicated that is executed at the same time every day or every other day and takes advantage of the gastrocolic reflex by following a meal. Digital rectal stimulation performed by the patient or caregiver is often helpful. Features of a neurogenic bowel must be addressed, because constipation leads to haemorrhoids and prolonged bowel movements expose the skin to significant pressure and possibly shear injuries, thus contributing to pressure ulcers. Moreover, the experience of incontinence can lead to social avoidance and isolation.

Neurogenic bladder

Bladder function becomes abnormal in 80–95% of patients, often during the secondary progressive stage, but is a problem at the onset in 10%. Its early presence is an unfavourable prognostic sign. Clinical features include urgency, hesitancy, dribbling, need for double voiding, recurrent urinary tract infections (UTI) and incontinence. The last can lead to embarrassment and withdrawal from the workforce and social interactions. Neurogenic bladder results from detrusor hyperreflexia (small, spastic bladder) with urgency and frequency in two-thirds of patients, detrusor atonia and hyporeflexia (underactive bladder) in one-third and impaired coordination between the detrusor and the sphincter muscles (detrusor–sphincter dysynergia, DSD) in 50%, with the detrusor contracting against a contracted sphincter. Neurogenic bladder may coexist with prostate disease or pelvic floor weakness. Inability to void completely leads to high residual bladder content (post-void residual, PVR), which increases the risk of UTI, bladder stones and hydronephrosis. Whereas clinical features often do not permit a pathophysiological analysis, urodynamic studies can accomplish this and facilitate evidence-based treatment.

Pelvic floor exercise, Crédé manoeuvres, biofeedback and both cholinergic (e.g. betanechol) and anticholinergic drugs (e.g. tolterodine, oxybutinin) and botulinum toxin, depending on urodynamic findings, combined with alpha-blockers and testosterone inhibitors in men with prostate disease, are often beneficial, but side effects may limit optimal dosing. Urine acidification may be a useful adjunct to reduce the likelihood of infections. When these interventions are inadequate, external catheters, chronic indwelling and intermittent catheterization are options.

Diapers are almost never the right answer, but often reflect reality, owing to lack of awareness and resources, in particular in nursing homes and when the person with MS or the caregiver lacks the means or insight to choose other more labour-intensive options. Diapers result in near-constant exposure of the skin to moisture and the toxic properties of urine (and faeces), which can contribute to skin breakdown and recurrent UTIs.

While external catheters address male incontinence, high PVRs persist. Furthermore, many patients have difficulties keeping them on, which can result in unanticipatable (and thus particularly embarrassing) incontinence. Penile retraction, often in the setting of severe spinal cord disease, may make the placement of an external catheter impossible. If not used appropriately or undersized, external catheters can cause skin ulceration and damage to the glans (hypospadia).

Chronic indwelling catheters increase the risk of UTI and bladder stones. Intermittent catheterization (IC) is an appropriate long-term solution if hand dexterity and cognitive function are not an issue or if done by a caregiver, but carries a risk of urethral damage and infections. The development of prostate disease and urethral strictures may make IC difficult and traumatic. Suprapubic catheters are associated with a lower risk of UTI than chronic indwelling catheters but, like these, are linked to continuous bladder wall irritation and an increased risk of bladder stones and bladder cancer. Urine may continue to drain through the urethra, necessitating the use of an external catheter. Additional long-term options include various surgical diversion techniques such as an ileal bladder.

The threshold for testing for UTI in a person with MS and changing symptoms should be low. Blind antibiotic treatment on the mere suspicion should be instituted only after obtaining a urine culture. False-positive symptoms of a UTI are not rare. Frequent use of antibiotics carries the risk of selection of multi-drug-resistant organisms that require intravenous antibiotics.

Glomerular filtration rate is often reduced, possibly due to recurrent UTIs, antibiotics, ionic contrast agents, voluntarily reduced fluid intake in order to avoid incontinence and NSAIDs used for pain. This may be subclinical in many patients with MS but may become significant in the setting of comorbid diabetes, hypertension and vascular disease.

Sexual dysfunction

About 80–90% of men and 45–75% of women with MS have sexual dysfunction. The prevalence rises with age and disease duration. Sexual satisfaction is important regardless of age and contributes to a general sense of wellbeing. For issues of fertility readers are referred to other standard texts. Features reflect all components of the sexual response cycle including mood/affect, libido, arousal, lubrication/erection, ejaculation and orgasm. Sexual function may remain intact in the presence of neurogenic bowel and bladder. Causes of sexual dysfunction include involvement of crucial cerebral (frontal, temporal, parietal) and spinal cord (long tracts, sacral parasympathetic and thoracic sympathetic segments) structures. Much rarer manifestations include hyperlibidinism.[24] Sexual satisfaction is compromised by depression, poor sleep, pain and spasm, sensory loss in erogenous areas, poor partner relations and miscommunication. Patients' many concerns need to be addressed, such as urinary and bowel accidents during intercourse, inadequate personal satisfaction and pain during intercourse, for example from muscle spasms, and the dual role of a significant other as sex partner and caregiver. While involving the partner in the discussion, care must be taken to not violate the principles of privileged health information. When evaluating a person with MS and sexual dysfunction, contributory roles of disordered sleep, mood and affect, venous and arterial disease, smoking, sex and other hormones, neuropathy and medications[25] must be considered. Patient and partner education is crucial. The sexual response cycle and the importance of experimentation and communication with the partner must be discussed.[26] Sexual dysfunction due to sensory loss can be alleviated by masturbation, use of vibrators in addition to sensate focus and pleasure mapping. Oral sex may be a helpful alternative to penetration. Concerns about neurogenic bowel and bladder are addressed by timed voiding and defecation and by limiting fluid and caffeine intake before sex. Pharmacological options include lubricating jellies, sex hormones (in case of deficiency) and agents such as phosphodiesterase-5 inhibitors (PDEI5) and aprostadil. When one PDEI5 does not work at maximum dose, others should be tried. Adverse interactions with alpha-blocking agents and nitrates must be considered. The EROS clitoral therapy device, vacuum pumps and occasionally penile implants are other options. Important roles rest with counsellors in optimizing partner communication and with rehabilitation therapists in facilitating positioning and avoidance of muscle cramps during sexual activity in addition to pelvic floor strengthening exercises.

Other autonomic changes

In addition to bowel, bladder and sexual dysfunction, MS can entail cold, purple feet due to sympathetic vasomotor dysregulation, which must be differentiated from atherosclerosis and orthostatic hypotension, which can be compounded by medications and dehydration.

Cognitive involvement

Cognitive decline affects over 50% of individuals with MS. Particularly in an ageing person with MS, an extensive differential diagnosis must be considered, including Alzheimer and multi-infarct dementia, medication effects, sleep disorders, heart and vascular disease, thyroid dysfunction and cobalamin and folate deficiencies. MS-related cognitive impairment is mild in 50%, moderate in 40% and severe in 10%. When mild, it may not be apparent to the casual observer or during a routine mental status examination. Mild impairment can be present very early in the course of MS, including with clinically isolated syndrome. Deteriorating work performance and a history of motor vehicle accidents may be tell-tale signs. When prompted, patients or significant others may mention word-finding difficulties or cognitive deterioration in the later part of the day. In mild to moderate impairment, the underlying personality usually remains intact. Typical issues are impaired multitasking and creativity, losing things around the house, leaving appliances running, etc. Common problem areas include the speed and accuracy with which information is processed, attention, executive functions, learning and memory, visual–spatial processing, verbal fluency and word-finding difficulties. Comprehension usually stays intact, but may be slowed. Memory problems focus on recall and retrieval, whereas the ability to learn new information often remains intact. Characteristically, patients can compensate for deficits until cognitive dysfunction becomes severe.

Early neuropsychological testing can establish a baseline when dysfunction is subtle and provide useful comparison as the condition progresses. Testing identifies strengths and weaknesses and contributes to vocational rehabilitation, optimizes social function and provides a basis for

cognitive rehabilitation, which may make use of cueing, memory aides and exercises such as crossword puzzles. Adjustment at work may be beneficial, including providing an opportunity for a nap in case of cognitive fatigue and avoiding shift work.

It is the treating provider's responsibility to discuss whether a person with MS is capable of operating a vehicle safely. This discussion requires sensitivity, since loss of a driving permit can be a watershed event which compromises independence and self-perception and since the insight into the risk to oneself and others may be lacking. Patients must be made aware of alternative means of transportation, their rights under the ADA (Americans with Disabilities Act), local opportunities to access 'call-a-ride' or other not-for-profit organizations that may provide assistance. Social workers can assist patients in optimizing access to community resources. A formal driving evaluation is often indicated to assess both cognitive and non-cognitive impairment. Non-cognitive obstacles to driving such as inadequate limb function can be addressed by vehicle modifications. When a person's disability precludes accessing a regular vehicle safely, a wheelchair-accessible van may be required. Unfortunately, the cost of vehicle modification is often prohibitive.

There is evidence that cognition benefits from disease-modifying drugs, cholinesterase inhibitors and drugs otherwise effective for fatigue (amantadine and modafinil) and walking speed (aminopyridine).

Mood and affective involvement

With a 50% prevalence, depression is 2–3 times more common than in the general population and the risk of suicide is elevated sevenfold.[27] MS attacks may manifest with depression, confusion and psychosis. While demyelination, inflammation, atrophy and plaques in several brain regions are linked to depression, emotional disturbances also reflect the response to a potentially devastating illness that has an unpredictable course, can result in disability and chronic pain, isolation, loss of social status and independence, nursing home admission and can contribute to divorce. Depression may be a side effect of beta-interferons and corticosteroids.

Pseudobulbar affective disorder, also known as forced or pathological laughing and crying or involuntary emotional expression disorder, can be disabling. A quinidine/dextromethorphan combination can alleviate this symptom. Euphoria, despite significant neurological problems, is recognized as 'la belle indifference'. Irritability is frequently brought up by both patients and significant others and contributes to relational stress. Other manifestations of disinhibition may lead to embarrassing social situations.

Psychopharmacological treatment and counselling by professionals with experience and expertise with chronic neurological diseases is warranted. The choice of medications must not only consider that many such drugs are beneficial for coexisting pain, but also that they can worsen fatigue, alertness, cognition, constipation, urinary retention and sexual function.[25] Individual psychotherapy is a highly effective but greatly underutilized intervention in patients with MS and comorbid mental health problems.

Seizures and other paroxysmal manifestations

Although rare, seizures are twice as common as in people without MS and become more prevalent in the later stages. Although difficult to visualize with standard magnetic resonance technology, cortical plaques may function as epileptic foci. Other paroxysmal symptoms include restless legs, tic douloureux (trigeminal neuralgia), spasms, dystonias, periodic leg movements, drop attacks, and Lhermitte sign. For a review of therapeutic options, the reader is referred to standard texts.

Prognosis

Persons with RRMS and PPMS reach an Expanded Disability Status Scale (EDSS) score of 6 [unilateral assistance (cane or crutch) required to walk at least 100 m with or without resting] on average in 15 and 8 years, respectively.[1] Predictors of poor prognosis include male gender, frequent attacks early on, early motor or cerebellar dysfunction, a large number of T2 and enhancing lesions and early atrophy. Long-term use of disease-modifying drugs influences prognosis,[3,4] as do various polygenetic polymorphisms and immunological parameters. The life expectancy of a person with MS is correlated with disability and is about 7 years less than in the general population.[28] Pneumonia is a common cause of death.

Comorbidities

When a person with MS who is older or has had MS for a long time and permanent disabilities presents with a new or worse symptom or sign, providers must answer several challenging questions: Does the new clinical presentation represent a manifestation of MS? Or if unrelated to MS, does it emanate from the nervous system? Or does it reflect dysfunction of another organ or a side effect of one or several drugs? The differential diagnostic considerations of acquired conditions that must be entertained when a person initially presents with symptoms and signs suggestive of MS must continue throughout the patient's lifetime whenever there is a change or evolution in clinical presentation.[14] A common belief on the part of patients is that each and every symptom must be due to MS. For

instance, a person may contact the neurologist about a supposed MS attack manifesting as weakness and fatigue, after a week of diarrhoea, vomiting and limited oral intake for which no medical attention has been sought. Patients must be educated that they should not prejudge the cause of a medical issue but rather let their healthcare professionals sort things out. A patient's assumption as to the aetiology may result in possibly life-threatening delay of care such as when fatigue is thought to be MS related but in fact results from atrial fibrillation.

Worsening fatigue may also result from diverse conditions such as UTI, congestive heart failure, thyroid disease, insomnia, cobalamin deficiency, poor glucose control, renal failure or depression, or from non-adherence to drugs such as modafinil or amantadine or inappropriate use of prescription or street drugs.

Similarly, worse spasms or spasticity may reflect MS or intercurrent illnesses, in particular UTI. And in individuals with severe spinal cord involvement and paraplegia or tetraplegia, spasms, spasticity and fatigue may be the only manifestations recognized by the patient of a deep vein thrombosis or fractures that result from minimal trauma in the presence of severe osteoporosis.

There is mounting evidence that vitamin D impacts not only bone health but also immune regulation. Low levels have been linked to a higher risk of MS, relapse rate and MS progression.[10] The prevalence of insufficiency $<75\,ng\,ml^{-1}$ and deficiency $<25\,ng\,ml^{-1}$ in the general population and among people with MS is striking. Therefore, levels should be checked regularly, particularly in recognition of the decrease in serum vitamin D during fall and winter. Since vitamin D toxicity is minimal with adequate renal function and normal calcium levels, many healthcare professionals advocate supplementation to a target approximately $50\,ng\,ml^{-1}$, often together with calcium. This practitioner treats deficiency with ergocalciferol 50 000 U weekly, followed by a repeat level which then governs continued care, including of insufficiency, with vitamin D 2000–4000 U daily.

Bone density is commonly decreased because of steroid and other medication use, low sun exposure (due to heat sensitivity and mobility problems) resulting in vitamin D deficiency, sedentary lifestyle and possibly autonomic and hormonal imbalances. Bone densitometry should be performed at regular intervals in men and women with MS and abnormal findings must be treated aggressively.

Several studies have characterized the link between tobacco use, risk of MS and of MS progression and EBV exposure.[8,11,29] Although proof of causality is difficult, there is sufficient evidence to warrant a very strong ongoing emphasis on cessation with any user who has MS.

Individuals with a sedentary lifestyle, elevated body mass index and history of steroid use are at increased risk of impaired glucose tolerance, which has been shown to affect peripheral and central nervous system function. Certain drugs, such as tricyclic antidepressants, elevate blood sugars. Individuals who use crutches or wheelchairs are at increased risk for upper limb nerve entrapment, which can also compound functional deficits due to MS. The presence of focal and systemic neuropathies may not be easily ascertainable by symptoms alone, given pre-existing sensory abnormalities due to MS. When history and examination suggest neuropathy, a work-up entailing laboratory tests, including glucose tolerance and glycosylated haemoglobin assays and electrodiagnostic studies, should be done.

Individuals with advanced MS or with spinal cord lesions and paraplegia or tetraplegia are at high risk for pressure ulcers. Cognitive impairment, non-adherence to pressure relief regimens, obesity, smoking, incontinence, dependent leg oedema and inadequate care at home, in nursing homes and in hospitals are contributing factors. Not infrequently, patients, caregivers and healthcare professionals underestimate the extent of pressure ulcers. If not treated early, their care can require many months of hospital care. Optimal care is often only available from providers with expertise not just in wound care but also in the specialized medical issues of individuals with paralysis.

Complementary and alternative medicine (CAM)

Surveys indicate that over 50% of people with MS have used therapeutic modalities such as antioxidants, low-fat diet, omega-3, high-dose vitamins, acupuncture, yoga, tai chi and countless others.[30] Their benefit in a given patient is difficult to assess given the placebo effect and the fluctuating nature of MS symptoms. Many studies are under way that seek to prove efficacy. It is important to convey to the patient that the provider is open to discussion and guidance regarding this approach. If the subject of CAMs is not out in the open, providers may not realize that a patient is non-adherent to prescription drugs and relies solely on CAMs. The provider may be unaware of ill-advised choices. Some patients resort to bee-sting therapy, which, likely via the introduction of foreign protein, may activate the immune system; others use high-dose vitamin B_6 (pyridoxine), which can (like the deficiency state) compromise neurological function. Many patients use cannabinoids, which can contribute to sedation when combined with prescription drugs that affect the CNS. It may be a violation of the law to prescribe controlled substances to patients using illegal substances. Also, patients may spend extraordinary amounts of money on ineffective or counter-productive medications and dietary supplements.

Access to healthcare

In regards to accessing health care, the combination of multimorbidity, mounting disability, cognitive decline, depression, loss of independence in activities of daily living, and shrinking social networks can be extremely challenging. While difficult in an urban setting, difficulties may be impossible to overcome in rural communities. This situation compromises the delivery of general health care, and even more so that of preventive medicine and mental health care.[31] Problems are compounded by the often limited ability to remember and appreciate the need for multiple appointments, lack of sufficient insurance coverage for specialists and drugs, great distances to providers, dearth of accessible transportation and doctors' offices, and limited expertise of many providers regarding the specific needs of patients with MS.[32] Referral to a multi-disciplinary team that offers 'one-stop-shopping' to patients may be helpful.

Fostering healthy living and resilience

The ability to adapt to acute illness and disease progression is referred to as resilience. Being self-confident and feeling good about oneself is a quality that fosters recovery from relapses in addition to adaptation to disease progression. It is important for people with MS to assume responsibility for their lives and take charge of their health. This means being educated about MS and other medical problems and their treatment and coming to medical appointments prepared with a list of issues, questions and goals to discuss.

Resilience comes naturally to some, but can also be learned. Many patients require assistance with emotional coping in order to avoid the negative feelings that can contribute to the physical features of MS. Recurrent themes that patients will voice include the uncertain prognosis, grief over the disability and other limitations linked with MS, the changing self-image and the social and physical accommodations needed from the patient, family and friends. Appropriate self-appraisal (e.g. effective and able versus powerless) is vital for successful adjustment to the uncertainty.[33] Counselling often allows patients and significant others to acquire such coping skills and improve their quality of life.

Educating patients about the benefits of healthy living may give them a sense of control and empowerment and motivate them to engage in tobacco cessation and regular (adapted if necessary) exercise with its benefit to mood, neuronal integrity and function, cognitive training, weight control and ultimately higher quality of life.[34]

Key points

- Persons with multiple sclerosis have increasing disability with ageing.
- Glatiramer acetate and beta-interferons are disease-modifying drugs.
- Generalized fatigue is present in two-thirds of persons with multiple sclerosis.
- Neurogenic bowel and bladder occur commonly in multiple sclerosis.
- Depression and cognitive impairment are common concomitants of multiple sclerosis.

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SECTION 7

Dementia and Cognitive Disorders

CHAPTER 71

Delirium

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Overview

Delirium is a dangerous diagnosis. It is common; it is commonly missed; and it is associated with several adverse outcomes. Although most clinicians label patients with delirium as having an 'acute change in mental status', the formal diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-Text Revision) paints a more complete and descriptive picture of these patients if put into sentence form: 'A sudden onset of impaired attention, disorganized thinking or incoherent speech. The patient usually has a clouded consciousness, perceptual disturbances, sleep–wake cycle problems, psychomotor agitation or lethargy and is disoriented'.[1]

History and pathophysiology

Although the term 'delirium' was not used, references to patients with delirium date as far back as the time of Hippocrates. Delirium has only attracted attention as a syndrome or a diagnosis in the past three decades, with the first textbook dedicated solely to delirium being published in 1980.[2] The reasons for this long misunderstanding of what to call this constellation of symptoms are related to the various ways in which delirium can present (hypoactive, hyperactive or a combination of the two) and the complex pathophysiology that causes such a variety of presentations. Although research into the pathophysiology of delirium is in its infancy in clearly defining the contribution each neurotransmitter system and biochemical mechanism has on the clinical picture of delirium, one proposed pathoaetiological model of delirium (Figure 71.1) is important in helping clinicians understand the complexity of a patient with delirium.[3] By keeping the complex systems and mechanisms in mind when trying to diagnose or manage a patient with delirium, clinicians will better be able to understand the challenges in making an accurate diagnosis (especially in the face of dementia) and the significant limitations that medications have in the 'treatment' of delirium.

Prevalence and incidence for various sites and situations

Delirium is one of the most serious illnesses that patients can have or develop and one that clinicians should not miss at the reported rate of 32–66%.[4] Typical rates of delirium on admission to a medical unit are between 20 and 30%. In a thorough systematic review of 42 studies meeting selection criteria with a focus on medical inpatient settings, only eight performed delirium assessment within 24 h of admission. The prevalence of delirium on admission among these well-performed studies ranged from 10 to 31%, but the low 10% was thought to be an underestimate as this study had strict selection criteria. In the same systematic review, the incidence during hospitalization among 13 studies was 3–29%.[5]

In general, surgical patients have been found to have higher rates of delirium than medical patients. In a review of primary data-collection studies, Dyer *et al*. found that rates are highest postoperatively among coronary artery bypass graft patients, ranging from 17 to 74% (>50% in five of the 14 studies reviewed).[6] They also found that rates among orthopaedic surgical patients ranged from 28 to 53% (>40% in five of the six studies). Of the two urological studies reviewed, rates ranged from 4.5 to 6.8%. Past biases have blamed anaesthesia agents for most cases, which wrongly have kept alive the belief, like that in the case of the intensive care unit (ICU), that delirium is unpreventable. Several studies which have evaluated the association between routes of anaesthesia (general, epidural, spinal, regional) and the risk of postoperative delirium have found that the route of anaesthesia was not associated with the development of delirium.

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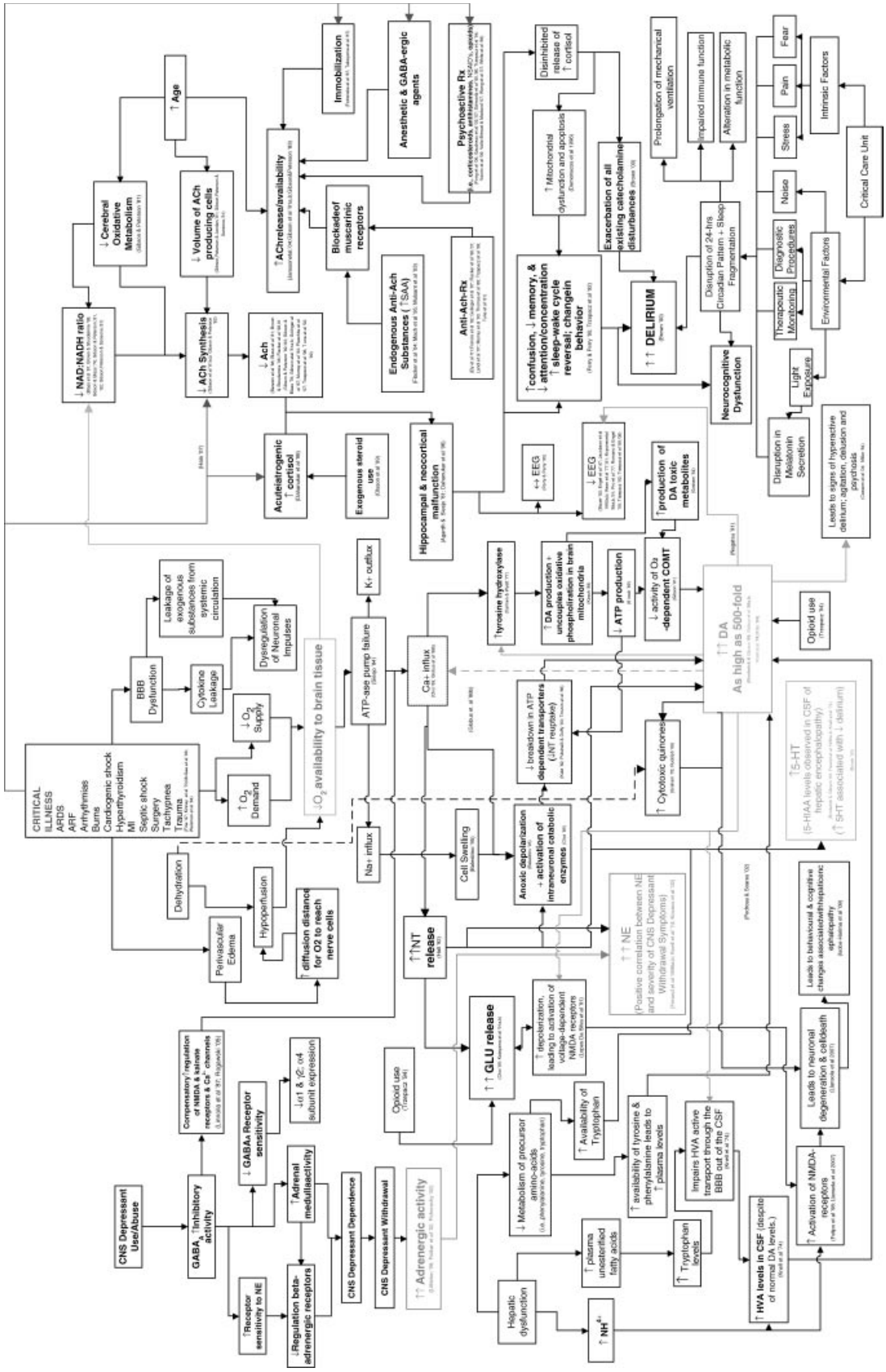

Figure 71.1 The pathoetiological model of delirium. Reprinted from Maldonado JR (2008).[3] Copyright (2008), with permission from Elsevier.

One of the sites with the highest rates of delirium, but perhaps the most controversial because of so many complicating factors, is the ICU. Rates as low as 19% and as high as 80% have been found.[7,8] For years, however, people have ignored these facts, have called it inevitable and unpreventable and have even labelled it 'ICU psychosis' so as to blame it on the ICU.

Discharge or 'transition' of patients out of the acute hospital setting has seen many changes over the past three decades. Data from post-acute care facilities (under such names as subacute-care facilities, skilled nursing facilities, rehabilitation centres and long-term care facilities) reveal two major issues: patients are discharged from acute hospitals with persistent delirium and delirium at these sites persists for an extended period of time. Kelly *et al*. found that 72% of 214 nursing home patients who were hospitalized for delirium still had delirium at the time of discharge back to the nursing home. The delirium persisted for 55% of the patients at 1 month and 25% at 3 months after discharge.[9] Marcantonio *et al*. found that 39% of 52 patients with hip fractures were discharged with delirium, which persisted for 32% of the patients at 1 month and 6% at 6 months after discharge.[10] In a large study of over 80 post-acute care facilities using the Minimum Data Set (MDS) to identify patients with any symptoms of delirium, Marcantonio *et al*. found a prevalence rate of 23% on admission. Among these patients, 52% still had the symptoms at 1 week follow-up.[11]

Two studies that looked at point of prevalence within nursing facilities discovered a similarly high rate of delirium. Mentes *et al*. evaluated 324 long-term nursing home residents using the MDS and found that 14% of patients had delirium.[12] Cacchione *et al*. prospectively evaluated 74 long-term nursing home patients and identified 24 (33%) with delirium.[13] While neither study could determine whether the delirium was a persistent one after a hospital stay or was an incident (new episode of) delirium, it is evident that delirium is common among nursing home residents.

Home care is an understudied site concerning delirium. However, two studies (detailed in the section 'Prevention and management interventions') showed lower rates of delirium among ill, older persons cared for at home compared with similarly ill, older persons cared for in the hospital. It is unclear whether something positive is being done in the home that prevents delirium or whether something negative is occurring in the hospital that contributes to the development of delirium.[14,15]

Associated adverse outcomes

Data about the adverse outcomes associated with delirium mainly come from studies of older patients in the hospital setting. Here, delirium has been found to be associated with hospital complications, loss of physical function, increased length of stay in the hospital, increased instances of discharge to a long-term care facilities and high mortality rates. Mortality rates for hospitalized delirious patients have been reported to be 25–33%, as high as the mortality rates for acute myocardial infarction and sepsis. There has been some question in the past about whether delirium was independently associated with these adverse outcomes or whether it was merely a marker of severe illness and physical frailty, since most studies identified older age, underlying cognitive impairment, severe, acute and chronic illness and functional impairment as the predisposing factors. However, when adjusting for these factors, delirium has been found to be independently associated with poor outcomes in most studies.

Associated adverse outcomes among delirious ICU patients have shown prolonged ICU stay, prolonged hospital stay and increased mortality compared with patients without delirium.[7,8] Data from post-acute facilities have also shown associated adverse outcomes, related to loss of physical function and mortality.[9,11,13]

The comprehensive approach to delirium

In order to improve the adverse outcomes associated with delirium, it is not enough just to improve our skills in diagnosing delirium and treating the underlying medical causes. The following are the necessary components of a comprehensive approach for those involved in the care of older persons and healthcare systems that interface with older persons:

1 *Awareness*: Be aware of how commonly delirium occurs and where it occurs and get others involved in the care of older persons to do the same.

2 *Diagnosis*: Know why it is important to differentiate and how to differentiate between delirium and dementia.

3 *Evaluation*: Identify and treat the underlying causes of delirium.

4 *Prevention*: Implement strategies or care systems that can prevent delirium.

5 *Management*: Manage patients who develop delirium.

Although there are no available studies to date that implement all five interventions, a multifaceted approach is warranted because of the nature of this multifactorial problem.

Awareness

Delirium should become part of the medical jargon for all who care for older persons. Furthermore, given the frequency with which delirium is seen and the seriousness of this diagnosis, a vital sign for mental status has been recommended,[16] and rates of incidence and outcomes

associated with delirium could be considered as quality-of-care measures.

Diagnosis

Delirium is not dementia. There is no difference in the core features of delirium in the DSM-IV-TR version compared with the previous version, DSM-IV, except that the DSM-IV-TR version recognizes that delirium can arise during the course of dementia.[1] Although this appears to be a minor detail, the message that this gives to healthcare professionals is a critically important one: '*delirium is not dementia*'. Most types of dementia have a progressive downhill course. Delirium should be considered reversible. A mislabelling or lack of differentiation between these two diagnoses is thought to be the reason why delirium is missed by physicians and by nurses. Misdiagnosis or late diagnosis may also partly explain why delirium is associated with adverse outcomes. Table 71.1 details some of the differentiating characteristics between delirium and dementia, based on DSM criteria, keeping in mind that one of the criteria not in Table 71.1 is that delirium must occur in the context of a medical illness, metabolic derangement, drug toxicity or withdrawal.

Altered level of consciousness (LOC) is an excellent clue in differentiating delirium and dementia because it is not always possible to know the patient's baseline mental status. Without ever having seen the patient before, one can determine whether the patient's LOC lies towards the agitated or vigilant side of the spectrum of LOC or towards the lethargic, drowsy or stuporous side of the spectrum.

One can ask orientation questions, but since disorientation and problems with memory are present in both delirium and dementia, the key in determining delirium from dementia is *how* the patient answers. The delirious patient will often give disorganized answers, which can be described as rambling or even incoherent.

The classic identifiers of delirium are acute onset and fluctuating course, both of which are usually obtained by close caregivers (family or nurses). Although acute implies 24 h, the term subacute is used to emphasize that subtle mental status changes can be overlooked by caregivers. Over a period of many days, the patient may appear to be slowly declining mentally due to the underlying dementia. If left unchecked, the initial delirium may impair other necessary functions, leading to further medical problems, such as dehydration and malnutrition, further complicating the delirium. This snowball effect explains in part why the aetiology of delirium is typically multifactorial. Therefore, if it is unclear how long the change has been occurring, patients should be put in the category of delirium and an evaluation should be made.

Attention is also one of the classic identifiers of delirium, which may often be helpful if the patient's baseline mental status is not known. It can be tested by having a conversation. Patients may have difficulty maintaining or following the conversation, perseverate on the previous question or become easily distracted. Attention can also be tested with cognitive tasks such as days of the week backwards, spelling backwards or digit span.

Psychomotor agitation or lethargy, hallucinations, sleep–wake cycle abnormalities and slow or incoherent speech can all be seen in patients with delirium, but these features are not necessary for the diagnosis.

Table 71.1 Differentiating delirium from dementia.

	Delirium	Dementia
Consciousness	Decreased or hyper-alert 'Clouded'	Alert
Orientation	Disorganized	Disoriented
Course	Fluctuating	Steady, slow decline
Onset	Acute or subacute	Chronic
Attention	Impaired	Usually normal
Psychomotor	Agitated or lethargic	Usually normal
Hallucinations	Perceptual disturbances May have hallucinations	Usually not present
Sleep–wake cycle	Abnormal	Usually normal
Speech	Slow, incoherent	Aphasic, anomic, difficulty finding words

Evaluation

General guidelines for the medical evaluation of patients are to consider all possible causes, proceed cautiously with appropriate testing and keep in mind that delirium is usually caused by a combination of underlying causes.

After a physical check and ascertaining the history, which includes obtaining details from anyone considered a caregiver (e.g. family, nurse's aide) and a thorough medication list, the mnemonic D-E-L-I-R-I-U-M-S can be used as a checklist to cover most causes of delirium (Table 71.2). Drugs are notorious for causing delirium. According to most authors in this area, 'virtually any' and 'practically every' drug can be considered deliriogenic. Several drugs have been found *in vitro* to have varying amounts of anticholinergic properties. However, since the pathophysiological and neurotransmitter mechanisms of delirium go beyond anticholinergic mechanisms, a more practical approach is to remember certain categories of medications that have been reported to cause delirium, some more common than others. The mnemonic A-C-U-T-E C-H-A-N-G-E I-N M-S is long, as would be expected, but highlights why

Table 71.2 Causes of delirium.

D	Drugs
E	Eyes, ears
L	Low O_2 state (MI, stroke, PE)
I	Infection
R	Retention (of urine or stool)
I	Ictal
U	Underhydration/undernutrition
M	Metabolic
(S)	Subdural

Table 71.3 Medications that can cause (have been reported to cause) an A-C-U-T-E C-H-A-N-G-E I-N M-S (mental status).

A	Antiparkinson drugs
C	Corticosteroids
U	Urinary incontinence drugs
T	Theophylline
E	Emptying drugs (e.g. metoclopramide, compazine)
C	Cardiovascular drugs
H	H2 blockers
A	Antibiotics
N	NSAIDs
G	Geropsychiatry drugs
E	ENT drugs
I	Insomnia drugs
N	Narcotics
M	Muscle relaxants
S	Seizure drugs

drugs are such a common cause of delirium (Table 71.3). In order to be as inclusive as possible and because many older reports did not discuss strict delirium criteria or such criteria were not commonly used, the following paragraphs describe not just delirium as a side effect, but also psychiatric side effects that might indicate presence of delirium, such as hallucinosis, paranoia, delusions, psychosis, general confusion, aggressiveness, restlessness and drowsiness.[17]

Levodopa (an antiparkinson drug) has been reported to cause mental status changes at a rate of 10–60% and include hallucinosis on a background of a clear sensorium, delusional disorders and paranoia. Abnormal dreams and sleep disruption may precede the more frank delirium symptoms and may be an early clue to their onset. Selegiline has been reported to cause mental status changes described as psychosis, aggressiveness and even mania.

Corticosteroids have been reported to cause 'psychiatric complications' in up to 18% of patients with doses above 80 mg per day. The mental status changes seen have been described as depressive/manic, an organic affective disorder with associated paranoid-hallucinating features and general 'confusion'.

Although short-acting urinary incontinence drugs have a greater potential to cause delirium, newer sustained release agents have also been reported.

Theophylline 'madness' probably meets delirium criteria. One of the first case reports described a patient with a toxic blood level that correlated with hyperactive periods marked by flailing of limbs, intense emotional lability, incessant crying and ripping out of intravenous lines and nasogastric tubes.

'Emptying' drugs is a reminder that drugs such as metoclopramide and droperidol that are often used for nausea and vomiting have potential for mental status changes. Reported mental status side effects include restlessness, drowsiness, depression and confusion. The mechanism is likely because of their antidopaminergic properties.

Cardiovascular drugs rarely cause mental status problems, but because they are so commonly prescribed for older persons, it is worthwhile to remember that some are more likely to cause problems, and also a few that have been reported in case reports. One of the first reports of confusion due to digoxin toxicity was over 100 years ago. Since then, reports of confusion even at therapeutic levels have been published. Antihypertensive agents that may cause mental status changes have primarily been reported in the literature through case reports. However, since they are so commonly used, it is worthwhile being suspicious about a few of them. These include beta-blockers (including in the form of eye drops), angiotensin-converting enzyme inhibitors and calcium channel antagonists.

H2 blockers, because they are primarily renally excreted and may have some H1 activity (antihistamine receptor subtype-1), may cause delirium, especially if patients have underlying risk factors such as renal insufficiency and dementia.

Antimicrobials, like cardiovascular drugs, rarely cause mental status changes, but are very commonly used; some examples worth being aware of are penicillin, erythromycin, clarithromycin, gentamycin, tobramycin, streptomycin, trimethoprim-sulfamethoxazole, ciprofloxacin, some cephalosporins and the antiviral acyclovir, particularly at high doses. Most reports propose that the mechanisms by which antimicrobials cause mental status changes are related to impaired renal function, drug–drug interaction and occasionally idiosyncratic behaviour. Several types of non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to cause delirium, even the selective cyclooxygenase-2 inhibitors.

'Geropsychiatric' medications are too large a category for an in-depth discussion, but a few comments are warranted to create some balance between reflexively blaming these drugs for the delirium just because 'any drug that works in the brain, can cause a problem in the brain' and understanding that although no centrally acting psychiatric medication is completely safe, certain ones may

be safer than others and psychiatric illnesses, especially depression, need to be treated. Tricyclic antidepressants (TCAs) can cause delirium with an overall incidence ranging from 1.5 to 20%. The highest rates, of course, seem to be among older, previously cognitively impaired and medically ill patients. Serotonin selective reuptake inhibitor (SSRI) antidepressants have a much safer side effect profile than the TCAs as far as delirium is concerned. However, one of the main side effects of SSRIs, hyponatraemia, can present as delirium in older persons. This has been reported with fluoxetine, fluvoxamine, paroxetine and sertraline. Although frank delirium due to SSRIs is rare, most reported cases seem to point towards drug interactions as a plausible cause. However, to emphasize that no centrally acting drug is completely safe, in a study of 10 healthy volunteers, paroxetine increased ratings of confusion and fatigue. There are also case reports of confusion due to antidepressants such as mirtazapine and venlafaxine. SSRIs alone and combinations such as sertraline and tramadol (a mu-receptor pain medication), trazodone and buspirone, and trazodone and methylphenidate have been reported to cause symptoms similar to those described in the serotonin syndrome.

The use of benzodiazepines (BDZs) was associated with an increased relative risk of developing cognitive impairment in one study among hospitalized patients, even those with normal mini-mental status examination scores on admission. Postoperative use of BDZs has also been found to increase the risk of delirium. Short-acting BDZs, even in small doses, have been reported to cause problems and the clinician should be aware that withdrawal from BDZs in the elderly may also present as delirium, perhaps more so when discontinuing short-acting compared with long-acting BDZs. However, there are models of successfully withdrawing patients from BDZs and this should be attempted whenever possible.

Antipsychotics can cause delirium, even the low-potency antipsychotic agents. Whether the antipsychotic prescribed is considered a typical or an atypical antipsychotic, the clinician needs to keep in mind that none of these drugs have pure mono-neurotransmitter activity. Rather, they have varying degrees of activity, either agonist or antagonist to many of the neurotransmitters implicated in the pathophysiology of delirium, such as dopamine, acetylcholine, serotonin and histamine. Therefore, like other geriatric psychiatric medications, antipsychotic drugs can and should be considered as a potential cause of delirium. Patients with Lewy body dementia have an increased sensitivity to neuroleptics. The clinical challenge here is that sometimes it is difficult to differentiate between Alzheimer's dementia and Lewy body-type dementia.

The ENT drugs in the mnemonic are a reminder of the multiple drugs, in particular over-the-counter (OTC) medications, that are taken for respiratory or sinus illnesses. The most worrisome of these ENT medications are the combination formulas, which contain two and sometimes three or even four active ingredients. Antihistamines, particularly the drug diphenhydramine, can cause problems at high doses, at moderately high doses, after a first-time oral dose in compromised elderly patients and even with topical use. Mental status changes have been reported to occur at high doses, at low doses and even from overuse of nasal inhalation of common OTC decongestants such as pseudoephedrine, phenylpropanolamine and phenylephrine. Expectorants and antitussins are probably safe provided that they are only used by themselves. One of the most commonly used, if not overused, ENT medications is meclizine. It has the potential to cause mental status changes because of its central anticholinergic action at the chemoreceptor trigger zone. The anticholinergic properties were thought to be the cause of confusion and steady cognitive and functional decline in an older patient who had been on meclizine for 3 years. Within 1 month off the drug, the patient's function and mentation improved. When rechallenged, the patient had cognitive and functional decline within 1 week.

'I' is a reminder that medications used for insomnia because of their effect on sedation have the potential to cause varying degrees of delirium. Most OTC sleeping aids come under a multitude of brand names without specifying the potentially dangerous deliriogenic medications dyphenhydramine or scopolamine.

Narcotics can be used safely in older persons with little risk of developing delirium, but a few important details need to be remembered. Meperidine is particularly risky in older persons, likely due to the anticholinergic activity of its active metabolite normeperidine. The main problems associated with the use of narcotics are probably related to toxicity, overuse or overdosage in patients with impaired hepatic or renal function.

Muscle relaxant is a misnomer because these medications act centrally in the brain, not locally at the muscles. Some of the commonly used muscle relaxants include cyclobenzaprine, methocarbamol and carisoprodol and have been reported to cause delirium.

Seizure medications have been reported to cause various types of cognitive impairment, including drowsiness, agitation, depression, psychosis and delirium. The cognitive impairment is thought to be related to serum levels, but clinicians should keep in mind that most anticonvulsants are protein bound and if the patient's nutritional status is poor then there is potential that the amount of free drug will actually be higher than what is measured by the serum level.

In conclusion, although the list of medications that can cause delirium is long, the mnemonic A-C-U-T-E C-H-A-N-G-E I-N M-S can help clinicians recognize some of the more common and some of the rare offenders. For patients

who present with delirium or for patients who are at risk for delirium, the following general guidelines concerning medication management can be used:

1 Use non-pharmacological interventions whenever possible instead of a medication.

2 Do not treat vague symptoms with a medication (for example, do not routinely give H2 antagonists for vague gastrointestinal complaints).

3 Include an assessment of OTC medications as potential offenders.

4 Evaluate all drugs for drug–drug and drug–disease interactions.

5 If a drug is started, decide on how long that drug will be used. The old rule of 'start low and go slow' needs to be expanded to 'start low, go slow and know when to stop'.

6 The justification for prescribing medications should be based on therapeutic reasons and not on preventive reasons and until the patient is no longer at risk for delirium or the delirium has resolved.

7 Do not treat adverse effects of drugs with another drug unless completely necessary (as may be the case with long-acting narcotics and laxatives).

The 'E' in the D-E-L-I-R-I-U-M mnemonic stands for emotions and reminds the clinician that depression can have psychotic features and as such may present similarly to patients with delirium. Although depression has classically been considered the masquerader of dementia, given some of the DSM-IV criteria for delirium such as disorganized thinking or psychomotor lethargy, depression should be considered a reversible cause of delirium.

Low O_2 (oxygen) states, 'L' in the mnemonic, should highlight to the clinician that older patients with acute cardiovascular or pulmonary illnesses can present with delirium. It could be said that 'delirium is as serious as a heart attack' because not only can the mortality rate of delirium be as high as that of myocardial infarction (MI) but also older delirious patients can have MIs that are commonly missed or present atypically. It is unclear whether patients, because of the delirium, cannot either describe or tell clinicians about chest pain or whether there exists a cardiocerebral syndrome in which the stress of the MI affects the adrenergic system causing a stress on the balance in the central nervous system, that is, in cognition. Not only are patients with stroke at risk of developing delirium as a complication of the stroke or the underlying comorbidities associated with the stroke but also delirium may be the presenting feature of some stroke patients.

Infections are one of the most common underlying causes of delirium among older people. The most common types of infections that cause delirium are urinary tract infections and respiratory infections. However, with the recent rise in antibiotic-associated diarrhoea due to *Clostridium difficile* bacteria, some clinicians have urged caution not to overdiagnose urinary tract infections that may be asymptomatic bacteriuria. Subtle infections such as cholecystitis and diverticulitis should be in the differential diagnosis. Although meningitis should also be considered, it is not clear whether or not cerebrospinal fluid analysis is warranted in the initial work-up of delirious patients without other symptoms that point towards a central nervous system infection.

Retention of urine and faeces can both cause delirium, although typically the presentations differ. Urinary retention causing delirium has been well reported in the literature under the term cystocerebral syndrome. The original report was of three cases, all involving older men who became acutely agitated and nearly mute. All three patients had large volumes of urine in their bladder and, in all three patients, the agitated delirium resolved within a short time after emptying the bladder. A proposed explanation is that the adrenergic tension related to the urinary retention might increase in the central nervous system and the consequent increase in catecholamines might produce delirium. Although this pathophysiological explanation has not been proven, clinicians should be very aware of this syndrome. One of the best ways to evaluate quickly for urinary retention is with a hand-held bladder ultrasound. Although the equipment has a fairly high initial cost, cost savings from the reduction in the use of straight catheterizations may help balance this issue.

Faecal retention as a cause of delirium has not been reported in the literature. However, since older patients, for multiple reasons, are at risk for faecal impactions, clinicians should be suspicious of this problem when the delirium is of the hypoactive type.

Ictal states are a rare cause of delirium and are not difficult to diagnose clinically for patients with tonic clonic seizures. However, patients who experience absence seizures may go unnoticed by caregivers and may only seem to have fluctuating mental status changes. Although an electroencephalogram (EEG) is not indicated in the initial medical evaluation of delirium, it should be considered when pertinent history is obtained.

Underhydration is used in the mnemonic, not only to emphasize the fact that dehydration can be one of the underlying causes of delirium but also to highlight the fact that those at risk for dehydration are at risk for delirium. Although there is much debate and consternation about which, if any, physical signs are pathomnemonic for dehydration among older persons, one quick method is to calculate the blood urea nitrogen (BUN) to creatinine ratio. Although there are several circumstances when the BUN/creatinine ratio may not be accurate, there are data to suggest that a ratio of greater than 17:1 puts the patient at risk for delirium.[18] Given this easy and commonly accessible parameter and given the data supporting the use of dehydration or difficulty with hydration as a target for

interventions, as will be seen below, dehydration should be considered to be at the top of the list as a contributing cause and not only as a risk factor for delirium and should be treated as aggressively as possible keeping in mind the limitations of each patient related to their cardiovascular status.

Undernutrition or malnutrition is rather complex and difficult to understand as a cause of delirium, most likely because, unlike other causes of delirium, it is less likely to be reversed quickly. It is evident, however, that malnutrition among hospitalized patients is not only common but also is associated with longer hospital stays, postoperative complications and even higher mortality. Clinicians and all healthcare providers in the hospital should be aware that restricted diets are likely to exacerbate malnutrition. Malnutrition is most directly related to delirium probably through the issue of medications that are protein bound. Patients who are malnourished may have lower protein stores and therefore protein-bound drugs will have a higher free concentration that puts the patient at risk for delirium. Other proposed relationships between malnutrition and delirium, which have yet to be fully elucidated, include those mechanisms looking at cytokines. Metabolic abnormalities that cause delirium are not difficult to identify because of the availability of commonly used laboratory tests. A complete metabolic panel will usually identify hyponatraemia or hypernatraemia, hypocalcaemia or hypercalcaemia and abnormalities of liver function or renal function. Thyroid function tests and vitamin B_{12} are typically put in this category.

Although delirium is not spelled with an 's' at the end, using the mnemonic D-E-L-I-R-I-U-M-S emphasizes to the clinician that delirium usually has more than one cause. The 's' also reminds the clinician that a subdural haematoma can cause a mental status change. Although the mortality rate of subdural haematomas among younger people is fairly high, the prognosis for older people is quite good provided that the diagnosis is not missed. The other difference between older and younger patients with subdural haematomas is that older patients may develop the subdural haematoma over a period of a few hours or days. Although there could be some debate as to whether or not all older patients presenting to a hospital with delirium should have some sort of brain imaging, most would agree that because this is a very reversible problem and which would cease to be reversible if the diagnosis is delayed, imaging should be considered if there has been a history of head trauma or falls or any suspicion that there was an unwitnessed fall.

One of the other causes of delirium not represented in the mnemonic is pain. Recognition of pain is improving, now identified as the *fifth vital sign*, and should be considered as a readily treatable cause of delirium, especially associated with elective surgery.

Prevention and management interventions

Before identifying which interventions are effective and which are not, it is important to understand the goals of interventions concerning delirium. They are (1) to prevent the development of delirium, (2) to reduce the adverse outcomes associated with delirium in those patients for whom delirium is not prevented and (3) to provide healthcare professionals with alternatives to physical restraints and pharmacological methods in the management of delirium. It is also important to emphasize that delirium is a complex issue related to the challenge of identifying who is at risk of developing it, diagnosing it if it does develop and getting other healthcare professionals to do the same. Interventions that are successful will involve several components, many of which are not easily measured. These include education about the risk factors and diagnosis of delirium, a 'culture' change about how *not* to use what seems logical and protective (for example, physical restraints or pharmacological sedation) and a realization that multicomponent interventions are not simple but can be done.

The most consistent message about successful interventions is to use an interdisciplinary team approach and follow geriatric principles. One of the most rigorous studies to date because of the assessment methods used and the close follow-up of patients was a prospective study of a multicomponent intervention to prevent the development of delirium in hospitalized older patients.[19] The study identified patients at risk for delirium on the basis of a previously developed predictive model. The study used the following six out of seven risk factors for the development of delirium: baseline cognitive impairment, eye or visual problems, altered sleep–wake cycle, dehydration, restricted or decreased mobility or hearing impairment (Table 71.4). The seventh risk factor, addition of more than three medications, was not used in the study, but is included in Table 71.4 for completeness (B-E-W-A-R-E). The standardized intervention protocols that were used in the study included the first six targeted interventions as described in Table 71.4 (P-R-E-V-E-N-T). Delirium developed in 15% of 426 usual care patients compared with only 9.9% of 426 intervention group patients [odds ratio (OR), 0.60; 95% confidence interval (CI), 0.39–0.92). The total number of days of delirium and the total number of episodes of delirium were also significantly lower in the intervention group, but the severity of delirium and recurrence rates were not significantly different. The interdisciplinary team included a specialist geriatric nurse, two specially trained persons familiar with the standardized intervention protocols, a certified therapeutic recreation specialist, a physical therapy consultant, a geriatrician and trained volunteers. The importance of this study is twofold. This study probably underestimates the success of a multicomponent intervention such as this because of the likely contamination that occurred

Table 71.4 Risk factors for delirium (B-E A-W-A-R-E) and targeted interventions (P-R-E-V-E-N-T) based on an intervention trial to prevent delirium.

B	Baseline dementia?
E	Eye problems?
A	Altered sleep–wake cycle?
W	Water or dehydration problems?
A	Adding >3 medications, especially sedating and psychoactive ones?
R	Restricted mobility?
E	Ear problems?
P	Protocol for sleep (back massage, relaxation music, decreased noise, warm milk or caffeine-free herbal tea)
R	Replenish fluids and recognize volume depletion
E	Ear aids (amplifier or patient's own hearing aid)
V	Visual aids (patient's own glasses, magnifying lens)
E	Exercise or ambulation as soon as possible
N	Name person, place and time frequently for reorientation
T	Taper or discontinue unnecessary medications. Use alternative and less harmful medications

throughout the hospital through implementing some of the standardized protocols. Since the study was done within one hospital, it was unable to randomize patients to separate floors and, thus, some intervention patients were on floors that also included patients from the usual care group. This was evident based on the 15% rate of delirium in the usual care group, which is lower than in previous studies.

A pre–post-intervention trial that focused on education of emergency department staff and admission to an acute geriatric unit ($n = 374$) showed positive results. The incidence of delirium decreased from 41% in the pre-intervention group to 22.7% in the post-intervention group at 4 months and 19.1% at 9 months.[20]

A few studies have targeted a very high risk group for delirium: older patients with surgical repair of hip fractures. Two randomized trials have focused on the prevention and management of delirium. In one study, 126 patients who were 65 years or older and admitted for surgical repair of hip fracture were randomized to geriatric physician consultation or usual care. The geriatric consultation was 'proactive', which meant that the consultation began preoperatively (for 61% of the patients) or within 24 h of surgery and a geriatrician made daily visits for the duration of the hospitalization. Targeted recommendations were made on the basis of a structured protocol emphasizing geriatric principles as well as postoperative medical care. Recommendations covered areas such as treatment of severe pain, elimination of unnecessary medications, regulation of bowel/bladder function (including discontinuing bladder catheters by postoperative day 2), adequate nutritional intake and early mobilization. The overall adherence rate by the orthopaedics team to the recommendations was 77%. Delirium developed in 32% of the 62 consultation group patients compared with 50% of the 64 usual care group patients (OR, 0.64; 95% CI, 0.37–0.98). There was a greater reduction in severe delirium, occurring in 12% of the consultation group and 29% of the usual care group (OR, 0.40; 95% CI, 0.18–0.89). Median length of stay did not differ in the two groups (5 days).[10] In the other study ($n = 120$), the multicomponent interventions were education of nurses, systematic screening, consultation by a nurse specialist and scheduled pain protocol. Mortality rates were inconclusive and there was no change in hospital length of stay (LOS) or physical function. However, there was a decrease in delirium duration and severity, but not incidence.[21] One randomized trial with a focus on just the management of hip fractures patients with delirium used multiple strategies for recognition of delirium, staff education, cooperation between orthopaedics and geriatrics and management of delirium and complications ($n = 49$). The study showed improved function and decreased duration and incidence of delirium in the intervention group.[22]

Randomized trials for the management of medical inpatients who already have delirium have not been as successful. Two trials utilized the same multicomponent intervention of systematic detection of delirium, a geriatric physician consultation with a geriatric nurse specialist doing follow-up. The first trial ($n = 227$) showed no change in mortality, LOS, function, discharge location or delirium duration.[23] The second trial ($n = 88$) showed no change in mortality, LOS or function, but there was a minor change in delirium severity.[24] A third randomized trial ($n = 174$) performed comprehensive geriatric assessments in the intervention group compared with a control group. It also utilized individually tailored treatment directed at the management of delirium, which turned out to mean that a significantly higher percentage of patients in the intervention group compared with the control group received physiotherapy, nutritional supplements, hip protectors, acetylcholinesterase inhibitors for underlying dementia and atypical neuroleptics for the delirium (and lower percentage of typical neuroleptics). The study showed no change in mortality, LOS or rate of institutionalization. Delirium was 'alleviated' significantly faster in the intervention group.[25] Finally, a fourth trial ($n = 400$) that focused on both the management and prevention of delirium was successful. A multicomponent intervention targeted staff education, assessment, prevention and treatment of delirium with an additional intervention towards the caregiver. The study showed a decrease in mortality (two versus nine deaths, $p = 0.03$), decrease in LOS (10.8 versus 20.5 days) and a decrease in the percentage of patients with delirium at day 7 (30 versus 60%).[26]

Another approach in the management of delirium is the delirium room (DR). The DR is a specialized four-bed

room to provide 24 h nursing care and observation by at least one nurse in the room and is completely free of physical restraints.[27] The hallmarks of the DR are the following. The four-bed DR is an integral part of an acute care for the elderly (ACE) unit. As such, the patients in the DR receive not only 24 h close observation but also the benefits of the geriatric principles for which the ACE unit has been shown to be effective in preventing loss of functional decline. Nursing inservices and protocols developed by nurses on how to identify and manage delirious patients are necessary. The DR is not isolated from the rest of the floor, rather it is the closest room to the main nurses' station. Having a location on the floor called the *Delirium Room* (see Figure 71.1) raises the awareness among healthcare professionals that delirium is a serious diagnosis, with serious consequences. Putting delirious or potentially delirious patients together in a room does not increase agitation as previous literature might suggest. Although the report of the DR was descriptive, it showed that over a 12 month consecutive time frame, out of the 69 patients with a diagnosis (according to the *International Classification of Disease*, 9th edition) of delirium in the DR, negative associations found in other studies of delirious patients were minimized. No physical restraints were used and only 29% of the patients received new orders for medications considered to be pharmacological restraints (haloperidol, risperidone or lorazepam), all at total daily doses of less than 2.0 mg. Only 13% of the patients lost physical function and none of the 69 patients died during their stay in the hospital. Mean length of stay for these patients was not significantly different compared with the length of stay for all other patients over the age of 70 years during the same time frame.[27]

Two studies of 'home–hospital care' have shown lower rates of delirium among medical patients cared for in the home compared with similar patients cared for in the hospital.[14,15] In the study by Caplan *et al*.,[14]100 patients with a mean age of 76 years (71% from home, 25% from nursing homes and 4% from hostels) with medical illnesses such as acute infections requiring intravenous antibiotics, deep venous thrombosis, minor cerebrovascular accidents or cardiac failure, were randomized within 24 h of diagnosis to either home or hospital. Although the researchers used the term 'confusion' instead of the formal diagnosis of delirium, they found a lower incidence of confusion (0 versus 20.4%; $p = 0.0005$) in the home group compared with the hospital group. Other geriatric complications were also found to be at a lower rate in the home group compared with the hospital group: urinary complications (incontinence or retention) (2.0 versus 16.3%; $p = 0.01$) and bowel complications (incontinence or constipation) (0 versus 22.5%; $p = 0.0003$).[14] The study by Leff *et al*.[15] identified older patients who required hospital-level care for pneumonia, congestive heart failure, chronic obstructive pulmonary disease and cellulitis. Of those who went home for treatments associated with hospital care, compared with patients who completed their treatments in the hospital (average length of stay 2.9 versus 4.9 days), the adjusted OR for incident delirium was 0.25 (adjusted 95% CI, 0.11 to 0.58).[15]

The take-home message for delirium is that although it is a difficult problem to prevent or manage when unpreventable, it can be done usually through a multicomponent intervention. No single simple intervention is likely to succeed and it is not possible to tease out which of the multiple components are having an effect and which are the detractors. Nonetheless, multicomponent interventions still need to be considered as the standard of care because delirium is such a complicated multifactorial problem.

Physical restraints

Physical restraints should not be used for patients who are at risk of developing delirium or who have already developed delirium (see Chapter 133, Restraints and immobility). The use of physical restraints is associated with developing delirium and is significantly related to severity of delirium. Furthermore, the proposed reason for the use of physical restraints among delirious patients, to prevent injury primarily related to falls, is misconceived. Of three studies of restraint reduction programmes in long-term care institutions, two showed no change in fall rate and one showed an increase in fall rate. However, all three studies showed a decrease in fall injury rates.[28–30] Of two studies in the hospital setting, restraint reduction was not associated with an increase in falls.[31,32] The rate of restraint use in the study by Powell *et al*.[31] went from 52 per 1000 patient-days to just 0.3 per 1000 patient-days. Although neither study reported injury rates before and after restraint reduction, Mion *et al*.[32] reported that injury rates after the restraint reduction programme were low. Importantly, they were modestly successful (≥20% reduction) in two of six ICUs in restraint reduction and reported that no deaths occurred as a result of a fall or disruption in therapy, including in the case of ICU patients on mechanical ventilators.[31,32] Furthermore, the fact that restraint-free environments can be achieved, as in some geriatric departments in European hospitals,[33] ACE units in United States hospitals[27] and some nursing facilities[34,35] adds to the evidence that restraint-free care should be the standard of care.

Pharmacological restraints

Currently, no antipsychotic or other pharmacological agent is approved by the US Food and Drug Administration (FDA) for the treatment of delirium. On the basis of the

available data concerning medications used in the management of delirium and the commonly accepted reason to use them (for patients whose behaviour interrupts the necessary medical care or puts themselves or others at risk of physical harm), antipsychotics should be considered a form of restraint until further evidence shows otherwise. Delirium is not analogous to psychosis. In patients with schizophrenia, antipsychotics can improve behaviour and function, with sedation being a common side effect. In patients with delirium, antipsychotics have not been shown to do this. It is argued that they control behaviour, but it is unclear whether this is through the sedation effects of the drugs or their effect on the neurotransmitters thought to play a role in delirium. To complicate matters further for older persons, one of the main problems with antipsychotic drugs, whether atypical or typical, is that they are not pure in their mechanism of action. For example, although risperidone primarily affects serotonergic (5-HT2A) receptors, it also affects to some extent dopaminergic and alpha-1 receptors. Although olanzapine affects the 5-HT2A receptors, similarly to risperidone, its sedation properties are probably due to its effect on the histaminic receptors. Clozapine also affects histaminic and muscarinic receptors and quetiapine has varying effects on histaminic and alpha-1 receptors and also has a small affect on dopaminergic and 5-HT receptors.

The available data for the use of antipsychotics in the management of delirium are poor because of the populations studied, types of studies done or the presence of the common mistake of not including a placebo group in order to measure the natural course (duration) of delirium without pharmacological intervention. As can be seen in Table 71.5, although several studies have examined the effects of antipsychotics in delirium, none of them were placebo controlled. It is important to note in the table the number of days when improvement is seen. Without a placebo-controlled group, it is unclear from the current evidence whether improvement in these studies follows the natural course of delirium or if it is from the use of the antipsychotic. It is evident from the lack of evidence that randomized placebo-controlled trials are needed. It should be noted that in a randomized controlled trial of a non-pharmacological intervention to prevent delirium, Inouye *et al*. found that even in the control group patients who developed delirium, the average total number of days of delirium was ~2.5.[19] Although this study did not go into detail about the percentage of delirious patients who received antipsychotics or the dose, another study[27] found that only 29% of 69 delirious patients received any form of pharmacological restraint (antipsychotics, benzodiazepines, sedatives/hypnotics) and this group had an average length of stay in hospital <5 days.

The proper dosages of antipsychotics have also never been established. One recent text recommends that if severe agitation is present, haloperidol doses of 0.25–1.0 mg can be used as often as every 20–30 min with a maximum 24 h dose of 3–5 mg. This dose is recommended because D2-dopaminergic receptors are saturated at low doses and therefore, theoretically, doses above 5 mg over a 24 h period are likely only to increase adverse events without providing additional clinical benefit. The goal should be an awake patient who is manageable, not a sedated patient, and the drug should be tapered and discontinued as soon as possible.

On the basis of the currently available data, the following conclusions can be drawn:

1 There is not enough evidence for the routine use of antipsychotic or other pharmacological approaches in the management of delirium.

2 On the basis of general geriatric principles, non-pharmacological interventions that have no or less risk should be tried before any pharmacological approach.

3 If pharmacological agents are used, the lowest possible dose should be tried first, keeping in mind the goal that is intended (patient manageable and awake, not oversedated).

4 On the basis of the very limited data, the category of drug of choice *seems* to be antipsychotics, not benzodiazepines or sedative-hypnotics.

Key points

- Delirium is common among older persons in the hospital, especially in surgical patients and patients in the intensive care unit (ICU) and in post-acute care settings, but not so common among patients with acute illnesses cared for at home.
- Delirium is a dangerous diagnosis and has been found to be associated with hospital complications, loss of physical function, increased length of stay in the hospital and ICU, increased incidence of discharge from the hospital to a long-term care facility and even higher mortality.
- The comprehensive approach to delirium involves awareness, diagnosis, evaluation, prevention and management. The causes of delirium can be remembered using the two mnemonics D-E-L-I-R-I-U-M-S and A-C-U-T-E C-H-A-N-G-E I-N M-S.
- Successful prevention and management interventions include a multicomponent intervention with protocols targeting risk factors to prevent the development of delirium, a geriatric consultation service for patients with hip fracture and a specialized four-bed room to provide 24 h nursing care, called the *Delirium Room*.
- Physical restraints should not be used in patients with delirium and rarely should pharmacological restraints be used.

Table 71.5 Available clinical studies examining the use of antipsychotics in delirium[a].

Study (methods)	*N* Mean age ± SD (years) (Age range, years) Type of patients	Drugs	Placebo?	Outcome and time frame (if reported)
Breitbart, 1996[36] (prospective, blinded, randomized)	30 39 ± 9 (23–56) All patients had AIDS	Haloperidol Chlorpromazine Lorazepam	No	DRS: average scores decreased from 20 to 12 by day 2 for haloperidol and chlorpromazine. Lorazepam: 'all patients had treatment limiting adverse side effects'
Nakamura, 1997[37] (prospective, open-label, randomized)	66 68 ± 15 vs 64 ± 13 (40–92 vs 23–86) Post-surgical and medical patients	Haloperidol Mianserin	No	DRS: 70% in each group improved by day 3 (DRS scores decreased from 22 to 10 in both groups)
Sipahimalani, 1998[38] (retrospective)	22 64 ± 20 (19–89) Psychiatric consults	Haloperidol Olanzapine	No	DRS: >50% reduction in scores 5/11 haloperidol group 6/11 olanzapine group Peak response[b]: 6.8 days haloperidol; 7.2 days olanzapine
Schwartz, 2000[39] (retrospective)	22 54 vs 58 (21–74 vs 19–91) Psychiatric consults; various medical illnesses	Haloperidol Quetiapine	No	DRS: >50% reduction in scores 10/11 in both groups Peak response: 6.5 days haloperidol; 7.6 days quetiapine
Kim, 2001[40] (prospective, open-label)	20 46 ± 18 (19–74) 11/20 patients had leukaemia	Olanzapine	No	DRS: >50% decrease in scores = 14/20 Peak response: 3.8 ± 1.7 days
Breitbart, 2002[41] (prospective, open-label)	79 61 ± 17 (range 19–89) Cancer patients	Olanzapine	No	MDAS: 76% had 'resolution' by day 7 according to MDAS <10
Sasaki, 2003[42] (prospective, open-label)	12 67 ± 15 Post-surgical and medical patients	Quetiapine	No	DRS: Japanese version: 100% had resolution (DRS-J <12) Average 4.8 ± 3.5 days
Kim, 2003[43] (prospective, open-label)	12 74 ± 4 (64–88) Medical patients	Quetiapine	No	DRS: 'stable' (not clearly defined) by 5.9 ± 2 days
Parellada, 2004[44] (prospective, open-label)	64 67 ± 11 Medical patients	Risperidone	No	DRS: 90% had DRS <13 by day 3
Han, 2004[45] (prospective, blinded, randomized)	24 66 ± 8 vs 67 ± 16 Mostly medical; some fractures	Risperidone vs haloperidol	No	MDAS <13: 42% risperidone vs 75% haloperidol (no significant difference) Average time to MDAS <13 was 4 days
Liu, 2004[46] (retrospective)	77 68 ± 10 vs 50 ± 15 (40–85 vs 15–77) Psychiatric consults	Risperidone vs haloperidol	No	'Recovered' based on 10-point visual analogue scale and two psychiatrists: 7 ± 4 days risperidone 8 ± 5 days haloperidol

Table 71.5 (*continued*).

Study (methods)	***N*** **Mean age ± SD (years) (Age range, years) Type of patients**	Drugs	Placebo?	Outcome and time frame (if reported)
Pae, 2004[47] (retrospective)	22 Mean 69 ± 10 (range 48–85) Neurosurgery, orthopaedic, oncology	Quetiapine	No	DRS: >50% decrease in scores: 19/22 Average scores from 22 to <15 in 7 ± 4 days
Lee, 2005[48] (prospective, open-label, randomized)	31 61 ± 18 vs 63 ± 15 Psychiatric consults	Amisulpride vs quetiapine	No	DRS-R-98: >50% decrease in scores 81% vs 80% 'Stabilization' based on DRS-R-98 in 6.3 vs 7.4 days
Straker, 2006[49] (prospective, open-label)	14 70 ± 11 (18–85) Medical patients	Aripiprazole	No	DRS: >50% decrease in scores 7/14 by day 5, 12/14 by day 7
Takeuchi, 2007[50] (prospective, open-label)	38 69 ± 10 Post-surgical and medical patients	Perisperone	No	DRS-R-98: >50% decrease in scores 27/38 Peak response: 5.1 ± 4.9 days

[a]Abbreviations: MDAS = Memorial Delirium Rating Scale. a 10-item scale integrating DSM-III criteria for delirium. Maximum score = 30. Scores of 10 or greater re consistent with delirium; DRS = Delirium Rating Scale, a 10-item scale integrating DSM-III criteria for delirium. Maximum score is 32. Scores of 13 or greater are consistent with delirium. DRS-R-98 = Delirium Rating Scale-Revised-98, a 16-item scale with a maximum score of 36. It is a revision of the original DRS by Trzepacz *et al.*[51]

[b]Peak response: number of days receiving an antipsychotic before achieving maximum response.

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CHAPTER 72

Memory clinics

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Introduction

Clinics specifically for the diagnosis and management of early dementia were first developed in the USA in the late 1970s. These were primarily research based, linked to developing Alzheimer's disease (AD) and ageing research centres and acted as a focus for expert assessment, investigation, treatment and advice.[1] Initially described as 'dementia clinics', the terminology soon changed to the more acceptable name of 'memory clinics' or 'memory assessment clinics'. Although the new titles are less stigmatizing, they run the risk of serving as a euphemism, avoiding an open and honest approach to the reality of dementia.

Predominantly service-oriented memory clinics were set up in the UK in the early 1980s,[2,3] offering multidisciplinary, outpatient-based assessment and diagnosis for mainly older people with memory and other cognitive problems, in an acceptable and accessible environment. At first, many of these clinics were funded from outside the National Health Service and were based mainly in university departments of geriatric medicine or old age psychiatry. Existing services tended to consider memory clinics to be a luxury, allowing academics to indulge their narrow clinical interests away from the reality of budgetary considerations and the priorities of practical dementia care. However, this reflected the concentration of service provision on dealing with the behavioural and psychological symptoms of advanced dementia and on crisis intervention and institutional-based management. The first memory clinics played an important role in raising awareness of the value of elective intervention and interdisciplinary care for people with early dementia and acted as a focus for the development of specialist knowledge and expertise in early diagnosis and management of people presenting with cognitive impairment.

Most of the early UK clinics were also very actively involved in research, especially recruitment into clinical trials of the emerging anti-dementia drugs. Largely thanks to the work of these centres, specific drug treatment for AD became available in the late 1990s and the focus of activity shifted towards the provision of an effective clinical service for patients presenting with memory disturbances and best use of medication, together with psychosocial interventions and patient and carer support and education.[4] The evolution of hospital-based memory clinics into more community-based memory teams was the natural consequence, working alongside or as an independent part of traditional mental health teams for older people.

Initially criticized for being too academic and isolated from mainstream practice, and ill-equipped to provide care after diagnosis, memory clinics have now become an integral part of quality dementia assessment and care services. The clinical guideline on the management of dementia published by the UK National Institute for Health and Clinical Excellence (NICE) and the Social Care Institute for Excellence (SCIE) in 2006 recommended the development of memory assessment services as the single point of referral for all people with a possible diagnosis of dementia.[5] They were seen as providing a responsive service to aid early identification, including a full range of assessment, diagnostic, therapeutic and rehabilitation services and an integrated approach to the care of people with dementia and the support of their carers, in partnership with local health, social care and voluntary organizations. The National Dementia Strategy in England, published in 2009,[6] suggested that memory clinics might form the core of new services for early diagnosis and identification of dementia in 'every town and city' in the country.

Although most memory clinics focus on the diagnosis of early dementia and mild cognitive impairment (MCI), some have a broader remit, whereas others target people with purely subjective memory loss or younger people with early-onset dementia or people with learning disabilities. Many concentrate on diagnosis and assessment with a view to best use of available medication and those in academic centres continue to conduct a lot of research, including clinical trials of newer drug treatments. The emphasis on assessment for drug treatment should not detract from

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the importance of providing the holistic, multiprofessional and multiagency approach to dementia care that should be central to the activity of all clinics.

Referral may be open access (those willing to see all-comers) or restricted to secondary or tertiary referrals or to selected individuals who meet predetermined criteria. In general, patients referred by their general practitioners (GPs) seem more likely to have dementia than self-referrals, although the reassurance given to those without organic disease (the 'worried well') should not be underestimated.[7] Memory clinics should never be merely rebranded old age psychiatry outpatient clinics or community-based services solely monitoring anti-dementia drugs.

Developments around the world

Memory clinics are now a feature of health services for older people in centres around the world, but they vary in terms of case mix, types of activity undertaken, whether they are primarily based in neurology, psychiatry or geriatric settings and their interface with other relevant agencies. Nearly all involve multiprofessional assessment, often with everyone coming together to share results in a diagnostic consensus meeting. The subsequent input into long-term support and follow-up can be very different, with some clinics seeing diagnosis and immediate care as the limit of their responsibility and others taking on the role of planning optimal long-term management. Memory clinics are sometimes the centre of a broad model of care, with preliminary home visits by a nurse and/or psychologist before clinic attendance and further home visits afterwards to discuss assessment results and plan future management.

In some countries, sometimes with government support, networks of clinics have developed to coordinate clinical, research and educational activity related to dementia. For example, in The Netherlands, memory clinics are well established and have led to the development of quality markers to facilitate description and comparison of activities and quality standards.[8] Most Dutch clinics actively involve the general practitioner, routinely provide a home assessment visit and have a strong research emphasis. In France, the national Alzheimer Plan has supported a major effort to ensure that each health district has its own memory unit (Consultation Mémoire) for dementia diagnosis and follow-up, building upon the expert memory clinics developed in the 1990s. At a regional level there are specialist Centres Mémoire de Ressources et de Recherche (CMRR), providing diagnosis in the most complex cases and delivering research and training. Other initiatives have included use of standard assessment and follow-up documentation, common educational projects and multicentre clinical research projects.

In Switzerland there is a collaborative group of memory clinics, enabling an active programme of education and training for health professionals and clinical research. The primary care doctor plays an important role in initial assessment before comprehensive diagnosis and treatment recommendations are made in the memory clinic, including memory training and caregiver support activities. There is also close involvement with the national Alzheimer's Association. The limited number of memory clinics in Germany and Austria are mainly university based and research oriented and are not covered by statutory health insurance, so have yet to become a standard component of local dementia care. In rural and isolated areas in Europe, the structures necessary to provide services are often lacking and novel approaches are therefore needed. For example, in Lapland there is a memory clinic bus which tours around offering memory testing and counselling services.

In the southern hemisphere, memory clinics providing multidisciplinary assessment and management for community-living people with dementia are developing in every continent, although still mainly based within the private sector or university centres in the larger cities. In Australia, a government-funded regional network of Cognitive, Dementia and Memory Services (CDAMS) were established in the 1990s across the state of Victoria, although elsewhere in the country the development of memory clinics has been more sporadic. The multicultural nature of Australian society presents particular challenges to ensure equity of assessment, service provision and utilization and highlights the need for clinics to be sensitive to the needs of people from a range of cultural and linguistic backgrounds,[9] a challenge also being addressed in many clinics in North America and Southeast Asia.

Why the need?

The worldwide growth in memory clinics has largely developed because of increasing demand and expectations of patients and families, frustrated by the difficulties of obtaining informed diagnosis and advice from existing services. They are not a replacement or alternative to these, but rather a more focused service providing a consistent approach to assessment, more specific diagnosis and a single resource for expert information and support (Table 72.1). Demographic changes are rapidly leading to greater numbers of patients with age-related cognitive disorders and there is appropriate reluctance to attribute forgetfulness merely to age. The growing awareness that memory failure is not inevitable and that effective intervention is available has led to a desire for comprehensive assessment, diagnosis, advice and treatment to be provided by professionals with specific expertise.

In many areas, existing services for diagnosis and management of memory disorders have been inadequate, with no clear professional responsibility and a widespread lack of specialist expertise and experience. There is a growing

Table 72.1 Potential benefits of memory clinics.

Benefits for patients and families
Non-stigmatizing, specialist resource breaking down potential barriers to recognition/diagnosis
Increases choice and improves patient experience and engagement
Expert multidisciplinary assessment and diagnosis of cognitive disorders
Ensures treatable conditions are not overlooked
Early identification of dementia and intervention
Anti-dementia drugs are effectively targeted, monitored and stopped as appropriate
Education and practical support for patients and carers
Empowers people with dementia while they are still able to maintain control over their lives
Provides advice on memory aids and memory training
Opportunities for counselling and psychosocial management
Improves quality of life by promoting and maintaining independence for as long as possible
Continuing care in the community may reduce need for institutionalization
Access to research studies
Benefits for service provision
Addresses growing demand for specialist diagnosis and treatment
Encourages earlier referral and multidisciplinary management
Develops awareness of dementia in primary care
Cost-effective way of significantly increasing the number of people able to be seen
Provides standardized assessment and diagnosis
Gateway to services
Efficient targeting and monitoring of scarce resources (including medication and psychosocial interventions)
Expertise in legal and ethical issues
Facilitates audit, planning and evaluation of services
Elective decisions may help to avoid crises in care
May reduce hospitalizations and lengths of stay
Postponement of institutionalization may reduce costs
Focus for professional education and research activity

appreciation of the complexity of the needs of these patients and that optimal assessment and management requires a multidisciplinary rather than a monodisciplinary approach.

Even in expert hands, assessment and management of mild cognitive disturbance are not always straightforward, with a difficult differential diagnosis ranging from the trivial to the very serious and from the easily reversible to the irreversible. Not all forgetful old people have dementia and not all demented old people have AD (Table 72.2). Comprehensive assessment reduces the chances of inappropriate labelling. There is a multiplicity of available assessment tools and investigations and, without access to the definitive diagnostic test of histopathology, some informed selection needs to be made. Once a working diagnosis has been reached, there is also a wide spectrum of available medical,

Table 72.2 Diagnoses to be considered in people presenting to memory clinics.

Neurodegenerative dementias
Alzheimer's disease
Dementia with Lewy bodies
Parkinson's disease dementia
Fronto-temporal dementia
Frontal variant
Primary progressive aphasia
Semantic dementia
Parkinson's-plus syndromes
Progressive supranuclear palsy
Corticobasal degeneration
Multiple system atrophy
Huntington's disease
Mild cognitive impairment (MCI)
Amnestic single-domain MCI
Amnestic multi-domain MCI
Non-amnestic single-domain MCI
Non-amnestic multi-domain MCI
Vascular cognitive impairment
Single stroke
Strategic infarct
Multiple cortical infarction
Multiple subcortical lacunes
CADASIL
Cerebral amyloid angiopathy (CAA)
Haemodynamic dementia
Neurological
Tumour
Normal pressure hydrocephalus
Multiple sclerosis
Motor neurone disease
Paraneoplastic
Mitochondrial encephalopathies
Learning disability
Post-traumatic
Subdural haematoma
Post-head injury
Dementia pugilistica
Functional/psychiatric
Depression
Anxiety
Stress and overwork
Adjustment disorder
Delusional disorder
Alzheimer phobia
Drugs/toxins
Prescribed medication
Alcohol-related
Substance abuse

(*continued overleaf*)

Table 72.2 (*continued*).

Endocrine/metabolic
Hypo-/hyperthyroidism
Hypo-/hyperparathyroidism
Hypo-/hyperadrenalism
Hepatic failure
Renal failure
Vitamin B_{12} deficiency
Thiamine deficiency/Korsakoff syndrome
Inflammatory
Rheumatoid cerebrovasculitis
Lupus cerebrovasculitis
Neurosarcoidosis
Infection
Post-encephalitis
HIV/AIDS
Neurosyphilis
Prion dementia (CJD)

psychological and social interventions that require tailoring to the individual.

The availability of specific drug treatment for AD and some other dementias and the need to identify suitable patients and to monitor drug efficacy are the most obvious justifications for early diagnosis. However, the emphasis on a medical model of care and the perceived influence of the pharmaceutical industry in driving forward the expansion of memory clinics should not detract from the broader psychosocial benefits of early recognition and intervention.

Although reversible dementia is uncommon, nearly all patients will have problems that can be helped and appropriate intervention can be instigated at a stage when it is likely to be most effective. A positive diagnosis reduces the risk of inappropriate management and avoids wrong assumptions being made. It empowers people with dementia to become involved in decision-making while they are still able to do so. The opportunities for forward planning may improve the psychosocial health of carers and also help to lessen the risk of crises in care at a later stage. Certainly a proactive approach is likely to be more efficient and also more humane than one that is crisis driven.

Are they effective?

In common with most health service developments, the rapid growth in memory clinics has occurred despite lack of evidence of effectiveness from randomized controlled comparisons with usual care. However, lack of evidence does not mean that they are ineffective and, given growing societal pressures and the considerable evidence on the effectiveness of the individual elements of memory clinics, the odds are in favour of their benefit.[10] A recent model suggested that memory services need only achieve a modest increase in average quality of life of people with dementia, plus a 10% diversion of people with dementia from residential care, to be cost-effective.[11] There is certainly evidence that community-living older people with cognitive impairment have fewer hospitalizations and nights hospitalized if their problem is diagnosed, compared with those who have never received such a diagnosis.[12]

Two completed randomized controlled trials have looked at the benefits of diagnosis of dementia in a memory clinic. A cluster randomized trial in The Netherlands showed that in comparison with usual care, an integrated multidisciplinary approach to dementia diagnosis in a hospital-based memory clinic setting increased health-related quality of life of the dementia patients for at least 12 months.[13] An Australian trial looked at the quality of life for carers of community-dwelling patients with mild to moderate dementia, who were randomized to attend a memory clinic or act as a control group. Those carers attending the memory clinic were found to have significant improvement in psychosocial health-related quality of life, particularly in the domains of alertness behaviour and social interaction, which was maintained at 12 months. However, there was no significant improvement in carer burden or knowledge of dementia.[14] The ongoing AD-Euro trial is comparing the clinical and cost effectiveness of post-diagnostic dementia guidance and treatment by memory clinics to usual care.[15]

Luce *et al*.[16] compared consecutive referrals to the memory clinic in Newcastle upon Tyne with referrals to the traditional and well-established old age psychiatry service in the same city. Memory clinic patients were younger, had lower levels of cognitive impairment and a wider range of diagnoses, with those diagnosed as having dementia being at least 2 years earlier in the course of the disease than those seen in the standard service. The authors concluded that memory clinics target a distinct patient group compared with traditional old age psychiatry services, identifying cases of dementia much earlier and having the potential to make valuable contributions to patient care in terms of access to treatments, services and support networks and in terms of obtaining information and preparing for the future.

Another British study in the more rural area of Dorset[17] compared consecutive new referrals to a memory clinic with consecutive new domiciliary requests within the same old age psychiatry service over the same period of time. The clinic patients had fewer behavioural and psychological symptoms of dementia, but were otherwise similar in demographic and clinical characteristics. Subsequently they were less likely to have a psychotropic drug prescribed, but were more likely to have documented risk management, care planning and follow-up, with a trend towards fewer moves into residential care and psychiatric ward admissions.

Surveys of memory clinic users' opinions of their experiences are generally very positive. van Hout *et al*.[18] used questionnaires with patients, relatives and GPs to measure their perception of the quality of care of an outpatient memory clinic. Positive opinions were recorded on the way in which the results were communicated, the usefulness of the assessment and the attitude of the clinicians. In contrast to GPs and relatives, patients were less positive about the clarity of the diagnostic information received and both relatives and GPs were negative on information and advice given to relatives. A subsequent study by the same researchers highlighted the importance of providing information not only on issues considered relevant by clinicians, but also tailored to the individual needs of patients and carers.[19] An Australian study of GPs' satisfaction with services provided by memory clinics also found them to be positive about the completeness and utility of the assessment and diagnostic information provided, but relatively less satisfied with advice regarding the family's coping and community support services for the patient.[20] It was considered that the service enhanced the capacity of GPs to provide ongoing care to people with dementia, but that the establishment of firmer communication and collaborative protocols between the clinics and GPs would improve their usefulness.

The memory clinic team

In order to provide a comprehensive service, memory clinics are characteristically multidisciplinary in nature, with a number of different professionals, each offering a particular expertise. Involvement is often based less on possession of any specific sub-specialist qualification than on interest and knowledge. In some centres the medical input may be from a geriatrician, in others from a neurologist and in others from a psychiatrist. Ideally there should be all three specialties involved. The other constant member of the memory clinic team tends to be a psychologist, not just to carry out neuropsychological assessment to aid diagnosis and management, but also to advise on and to undertake psychosocial interventions with both patient and family. Another invaluable team member is a specialist nurse, who can help with both the medical and psychological assessment and management. This can be carried out beyond the physical confines of the clinic, facilitating and reinforcing the process in the patient's own environment. Finally, dedicated administrative help is essential, not only to ensure the efficient running of the clinic, but also to cope with the forgetful patients who phone repeatedly to check the time of their appointments.

Beyond these core team members, there needs to be easy access to other professionals, such as speech and language therapists, occupational therapists and social workers. Increasingly there is also a need for someone competent to provide genetic counselling and advice to worried relatives. Developments in drug therapy suggest an important potential role for the pharmacist and newer diagnostic techniques may require greater involvement of radiologists and neurophysiologists. Volunteers and support workers from the local Alzheimer's Society are becoming closely associated with some clinics, providing additional practical support and counselling to newly diagnosed patients and their families.

The optimum size of the team is likely to be between four and seven, united by a common feeling of direction and purpose. Although each member should be able to identify the specific and general contribution they can make, a flexible working style which crosses conventional professional boundaries will provide greatest job satisfaction and most effective care for patients.

As in other aspects of geriatric practice, getting the multidisciplinary team to work effectively is essential for the smooth running of the clinic. Good teamwork takes time to develop and whoever is the team leader (usually the senior physician or psychiatrist) needs to strike a balance between over-structuring clinic activities and allowing individuals to function totally independently. The team will not work effectively when one particular professional (or profession) considers the guarding of their perceived area of expertise as a priority, setting up artificial borders which others fear to cross. A belief in the importance of professional hierarchies, concerns over territory and differences in terminology will act as barriers to effective care delivery and can lead to wasteful duplication of effort and apparently contradictory management advice. Individual members should be encouraged to view the value of their contribution as depending on the functioning of the whole team.

What happens in a memory clinic?

There would seem to be general agreement that a memory clinic can provide in one setting all the essential components of comprehensive assessment leading to diagnosis for older people presenting with memory problems, followed by appropriate interventions (Table 72.3). The assessment will include full history and medical examination, detailed neuropsychological and neurobehavioural assessment and appropriate laboratory tests and neuroimaging. Some clinics have a totally standardized approach, where everyone gets everything, whereas others will tailor the assessments to what is specifically indicated and what has not been done before. Whereas some clinics will restrict themselves to a one-off evaluation, confirming a diagnosis and perhaps recommending an appropriate intervention, others will aim to provide ongoing support and more comprehensive management. Certainly diagnosis divorced from effective intervention is likely to be unsatisfactory for all.

Table 72.3 Stages in memory clinic evaluation and management.

History (from patient and reliable informant), including functional and social background
Cognitive assessment (and mood)
Relevant physical examination
Investigations (including neuroimaging)
Formulate diagnosis and discuss appropriately (with patient and family with consent)
Provide relevant written information and contact details of local contacts
Consider management options:
• Treat comorbid medical conditions appropriately
• Review existing medication and consider anti-dementia drugs
• Ensure good nutrition and hydration
• Psychotherapeutic interventions
• Memory aids and problem-solving skills
• Safety issues (including driving) and promotion of independence
• Legal and financial/estate planning and eligibility for benefits
• Social interventions (home care, social clubs, respite)
• Carer education and practical and emotional support
Arrange appropriate follow-up

Clinics should be held close to the community they serve. Holding them away from the stigmatising settings of geriatric or psychiatric hospitals will help to encourage referral and attendance. Remembering to keep appointments is an obvious problem for this client group and sending reminders a few days before and asking people to confirm that they will be coming will help to reduce non-attendance. Forewarning people about how long the assessment will take is advisable. In some clinics assessments take all day, moving from one professional to another, and many patients find this tiring and cannot cooperate fully. Some psychometric tests need to be repeated at a set interval, so initial assessment will require more than one visit. Certainly, given the gravity of the potential diagnoses, a case can be made for all patients to be tested on at least two occasions a few weeks apart. We have found that a maximum of 60–90 min per visit (of which 30 min may be taken up with cognitive testing) is optimum.

Patients should be asked to come with someone who knows them well and can provide corroborative background. The presence of a close relative or carer will also help to ensure that advice and information provided in the clinic are acted upon. Ideally there need to be two clinic rooms, allowing an opportunity for patient and informant to talk separately to different team members.

History and medical examination

The essential first step in clinic assessment must be to obtain a detailed and accurate history. Cognitive impairment in elderly patients is often unrecognized. A patient who superficially appears alert, pleasant and cooperative and denies any significant symptoms is too often assumed to have no problems and mild dementia is easily overlooked. Establishing the reason for referral is a good place to start.

The onset and duration of symptoms are crucial and claims that difficulties date from some seemingly relevant event such as an accident, bereavement or hospital admission must not be accepted unquestioningly. Often a sudden change in circumstances merely draws attention for the first time to pre-existing problems. Changes in role are often of significance and questions should be asked about loss of competence in everyday skills and activities (e.g. driving, travelling away from home, handling correspondence and finances, taking medication regularly). The nature and progress of any changes should be established.

It is essential to take a history from both the patient and from a carer or friend (a neighbour may be of more value than an uninvolved relative) and specific examples of practical difficulties should be elicited. Associated mood disturbances, personality change and behavioural difficulties must be sought. Specific questions should be asked about delusions and hallucinations. Present and past consumption of alcohol, use of prescribed and non-prescribed drugs and the patient's general medical condition need to be established. A family history may give pointers to the diagnosis and sometimes explains a patient's excessive concern or apprehension. Much useful information is often available in previous medical records.

The Cambridge Mental Disorder of the Elderly Examination (CAMDEX) attempts to standardise the clinical information gathered in the course of a diagnostic interview with history being obtained from both the patient and a relative. Some details are therefore duplicated, but it serves as a useful starting place for those less confident in eliciting all the relevant issues. Informant questionnaires, such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) can be completed by relatives before clinic attendance as an aid to establishing their report of changes in everyday cognitive function compared with 10 years before. Numerous other assessment scales, for example of neuropsychiatric symptoms, depression, activities of daily living, quality of life and carer burden, are available[21] and can be incorporated into clinic practice. They are valuable as an objective basis for documenting change and as a source of data for audit and research.

A medical examination, with particular attention to the cardiovascular system, central nervous system and special senses (eyes and ears) is also required. This may help to elucidate the cause of the memory problems, may identify physical consequences of the condition (poor nutrition, neglected personal hygiene, signs of physical abuse) or may identify coexisting morbidities. Focal neurological signs will suggest vascular disease or a space-occupying

lesion and extrapyramidal signs will raise the possibility of Parkinson's disease or dementia with Lewy bodies (DLB). Primitive reflexes (e.g. palmo-mental, grasp, pout, rooting) are common in most forms of dementia, although not always easy to elicit. Myoclonus may be seen in prion disease, Huntington's disease and early-onset AD and muscle fasciculation may suggest motor neurone disease associated with fronto-temporal dementia (FTD).

Cognitive assessment

Following the history, an objective assessment of cognitive functioning is required. This will aim to establish strengths and weaknesses of a variety of functions relative to a standardized, norm-referenced scoring system. In this way, the nature and extent of cognitive deficits can be determined, informing diagnosis and management and acting as a comparator for past and future assessments. Ideally an experienced psychologist should undertake testing, although much useful information can still be obtained by any suitably trained professional. The Addenbrooke's Cognitive Examination Revised (ACE-R)[22] is an easy to use and acceptable screening measure with good sensitivity and specificity in clinic settings and incorporates the Mini Mental State Examination (MMSE) and clock face drawing. A simple screen of executive function, such as verbal fluency, will help to identify subcortical deficits. When possible, assessment should be made of premorbid intellectual status, to assist in the satisfactory interpretation of other test scores. Tests must also be appropriately selected to take account of limitations imposed by deficits such as language impairment and dyspraxia. For example, recognition memory tests may reduce the demand on expressive language, normally required in recall memory tests. A standardized measure of mood is also desirable.

There is a very wide choice of psychometric tests suitable for use with memory clinic patients and choice will be governed by the main purpose of the examination and the time available, and also personal preference and experience. Computer-based assessment of cognitive function is becoming more available and has the advantage of being sensitive to small changes in performance and allowing detailed assessment of attention and motor responses. At present its use is still confined mainly to research settings. An outline of the assessments used routinely in the Cardiff memory clinics is shown in Table 72.4.

Whatever tests are chosen, they must be acceptable to the person being tested and with no content that belittles their adult status. Consent to the assessment procedure needs to be obtained and the tester should spend some time in explanation of the purpose of specific tests and be competent to answer queries regarding their usefulness and acceptability. Sensory and physical limitations should be accommodated as much as possible, by the provision of adequate lighting, additional specialist earphone amplifiers, suitable seating and minimum distractions. During testing, realistic reassurance should be provided, with feedback phrased positively to highlight strengths as much as weaknesses. At the end of testing, patients should be given an opportunity to make their own observations on their performance.

Table 72.4 Cognitive tests commonly used in the memory clinics in Cardiff.

Premorbid ability
National Adult Reading Test (NART)
Cognitive screen/test battery
Mini-Mental State Examination (MMSE)
Addenbrooke's Cognitive Examination Revised (ACE-R)
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Frontal Assessment Battery (FAB)
Specific cognitive abilities
Story recall (immediate and delayed)
Irving Names Learning Test (NLT)
Kendrick Cognitive Tests (object learning and digit copying)
Rey–Osterrieth Complex Figure Test (ROCF)
Clock drawing
Verbal fluency (controlled oral word association test and category)
Trail-making Test A and B
Graded Naming Test (GNT)
Mood
Geriatric Depression Scale (GDS-15)

Observations of the person's concentration, cooperation, anxiety and motivation during assessment should be carefully weighed against performance. The approach of the patient to each test and his or her satisfaction with the outcome is often as revealing as the particular score obtained. Results should be considered in the context of the patient's previous education and experience, their age and presence of sensory impairments and comorbidity and diagnostic cut-offs for each score treated as guides rather than absolutes. In particular, a 'normal' score does not exclude the possibility of significant problems, including dementia. In such cases, more detailed testing will often reveal minor detriments in a range of tests, which are inconsistent with the patient's expected level of functioning. It is nearly always desirable, and sometimes essential, for assessment to be repeated at a future date in order to detect any progressive deterioration. Longitudinal follow-up increases the accuracy of diagnosis, particularly in mild dementia.

Laboratory tests

A routine screening battery of laboratory tests will be indicated in most patients when first seen.[5] These should

include a full blood count, urea and electrolytes, liver function tests, calcium and phosphate, random blood glucose, thyroid function and vitamin B_{12} and folate. A more extensive range of tests may be indicated in younger people with dementia and in those with atypical presentations or signs and evidence of systemic illness. These might include plasma viscosity or C-reactive protein and autoantibodies for inflammatory disease and tumour markers for malignancy and paraneoplastic syndromes. Syphilis serology is now not carried out as a routine, but still needs to be considered. Genetic testing, for example for apolipoprotein genotype, is not yet diagnostically useful, but may be rarely indicated to look for known APP and PS-1 and PS-2 mutations when familial dementia is suspected. It should only be undertaken after appropriate counselling, preferably in collaboration with a specialist genetics service.

An electrocardiogram is desirable in any patient with possible vascular disease and in patients with a bradycardia or history of dysrhythmia who are being considered for acetylcholinesterase inhibitor (AChEI) drug treatment. An electroencephalogram is rarely indicated, but may be useful in suspected encephalitis, metabolic encephalopathy, seizures or prion disease and in confirming the presence or absence of delirium, in which it is almost always abnormal. Examination of cerebrospinal fluid is indicated in patients with suspected infectious, inflammatory, autoimmune or demyelinating disease and is used in some centres to measure amyloid and tau levels to improve diagnosis of early AD and identify patients with MCI who are more likely to convert. In normal pressure hydrocephalus (NPH), lumbar puncture may help to predict suitability for surgery. Rarely, nerve conduction studies may help to diagnose FTD associated with motor neurone disease, muscle biopsy may be useful in mitochondrial disorders and even cerebral biopsy may be justified in suspected primary cerebral vasculitis.

Neuroimaging

The role of neuroimaging in the routine management of memory clinic patients is largely determined by its availability. Certainly neuroimaging no longer merely fulfils the negative role of excluding 'treatable' conditions that mimic or cause dementia, but contributes positively to differential diagnosis and provides useful prognostic information. Depending on availability, computed tomography (CT), magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) might all contribute to clinical care. Various other techniques are available in research centres. Recent diagnostic guidelines suggest that at least one structural CT or MRI examination should be made over the course of a dementing illness to rule out space-occupying or vascular lesions and that SPECT (or PET) may be used in cases of significant diagnostic uncertainty.[5]

Imaging with CT is probably the radiological investigation most often used in memory clinic patients, owing to its wide availability. It can show good detail of the brain structure and is especially useful in identifying dementia due to space-occupying lesions, hydrocephalus or large cerebral infarcts. Smaller lacunar infarcts are less easily seen and absence of infarcts does not exclude the possibility of vascular disease. Cortical atrophy is a common finding in older patients, not necessarily associated with clinically abnormal brain function. Some patients with AD will have a normal scan, but the presence of medial temporal lobe atrophy is usual. The presence of localized atrophy will also lend support to diagnoses of FTDs and focal syndromes such as posterior cortical atrophy. Overall, CT may be expected to impact on diagnosis and treatment in about one in eight of dementia cases.

MRI is less widely available, less tolerated by patients and more expensive than CT. However, contrast sensitivity and spatial resolution are better, even without the use of contrast agents, and it does not suffer from bone artefacts. Evidence of generalized atrophy is no more diagnostically useful than with CT, but measurement of the size of the hippocampus and entorhinal cortex plays an important role not only in diagnosis of AD, but also in identifying patients with mild cognitive impairment who are at risk of progressing to dementia. Smaller infarcts can be seen more clearly than with CT and MRI has the potential to detect focal signal abnormalities that may assist the clinical differentiation between AD and vascular dementia (VaD). Severe temporal lobe atrophy and hyperintensities involving the hippocampal or insular cortex are more frequently noted in AD. Basal ganglionic/thalamic hyperintense foci, thromboembolic infarctions, confluent white matter and irregular periventricular hyperintensities (leukoencephalopathy) are more common in VaD. Leukoencephalopathy involving at least 25% of the total white matter must be present to diagnose small-vessel cerebrovascular disease.

Functional imaging using HMPAO-SPECT allows regional cerebral blood flow to be visualized and quantified. In established AD there is a reduction of flow in mainly temporo-parietal regions, although this finding is inconsistent in the early stage of the disease when diagnosis is most problematic. In FTD, SPECT shows diminished perfusion anteriorly. In VaD, multiple focal deficits may be seen. FP-CIT SPECT distinguishes DLB and Parkinson's syndromes from AD. PET scans are largely limited to research centres. FDG-PET shows characteristic alterations in cerebral glucose metabolism early in AD and FTD. PET imaging of amyloid binding (PIB-PET) appears to be highly sensitive and specific for AD, even at preclinical stages. This seems likely to play an important role in diagnosis and treatment decisions in future years.[23]

What interventions can be offered?

At the very least, patients assessed in memory clinics should receive an informed discussion of their diagnosis and prognosis, with arrangements made for ongoing review, support and management. In a few patients, there will be a reversible cause for their symptoms (e.g. medication side effects, hypothyroidism, vitamin B_{12} deficiency, cerebral vasculitis, Wernicke–Korsakoff syndrome) that will respond to specific treatment. The proportion of patients with reversible dementia is probably less than 4%, but concurrent medical conditions causing mild cognitive disturbances are much more common and are potentially treatable.[24] Although treatment of these conditions may not always lead to complete resolution of cognitive symptoms, it is important to identify any concomitant conditions to avoid unnecessary disability and misdiagnosis.

Depression, whether primary or secondary, is especially deserving of energetic treatment, generally using a selective serotonin reuptake inhibitor (SSRI), such as citalopram or sertraline, or the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, that are free of significant cognitive side effects. Even in patients with established dementia, appropriate medical intervention may help cognition and slow progression of the disease. Control of vascular risk factors, especially hypertension, may favourably influence the clinical course of both degenerative and vascular cognitive impairment. Timely use of specific drug treatments for AD and probably VaD and DLB will give significant benefit to a majority of patients taking them.

Certainly all patients with cognitive difficulties and their carers will benefit from informed discussion about their problems and appropriate psychosocial interventions.[25] Advice can be given on the appropriate use of memory aids, memory training and specific psychological interventions for patients and families. Financial and legal advice will usually be appropriate and practical suggestions to help with problems of daily living and safety concerns, particularly the advisability of continued driving. Issues surrounding advanced directives are attracting growing attention. Meeting the needs of carers is also important, by providing information, individual counselling, access to support groups and respite care through contact with local Alzheimer's organizations and relevant community services.

Diagnostic disclosure and meeting information needs

Most advocates for people with dementia and their carers now believe that, in most cases, patients should be told what is wrong with them, what the implications are, what can be done for them and what treatment is likely to involve. Breaking the news in a timely and tactful manner is an important role for memory clinic staff. Reactions of AD patients to being told their diagnosis include relief (as the diagnosis provides an explanation for their difficulties), disbelief (as they may lack insight and do not feel ill), loss (grieving for failing intellectual abilities and limitations in the future) and fear of becoming a burden. All can be satisfactorily addressed.

Practice of diagnosis disclosure amongst specialists is changing. In the 1990s, less than one-third of old age psychiatrists and geriatricians 'usually told' people with mild dementia their diagnosis, whereas recent studies report that a majority of specialists now regularly disclose diagnosis.

Memory clinic patients should be given the opportunity to learn as much or as little as they want to know about their condition, with information provided in a sensitive and measured way[26] (Table 72.5). Patients and carers both have individual needs and each should be addressed separately. In addition to clearly describing diagnosis, specific attention should be given to comprehensible and practical information about coping strategies, care services, likely course of the disease and treatment, specific drug treatment and follow-up. Wald *et al*.[27] proposed the 'rule of threes' for information provision to carers of people with dementia. At diagnosis, they want information about what dementia is, what medications are available and explanation about behavioural and psychiatric symptoms of dementia. At an early follow-up appointment, they want information about services, the course of the illness and what to do in a crisis. At a later follow-up appointment, they want information about support groups, benefits and financial and legal issues. At a later stage, they want information about psychological therapies, the effects of the illness on carers and complementary therapies.

Information giving is not only a medical responsibility. All members of the multidisciplinary team should consider every therapeutic encounter to be an opportunity for education and information provision. Dedicated time should be put aside during every memory clinic consultation for information provision – it should never be merely an after-thought at the end of the assessment. Verbal information should be backed up by written information, with recommendations for further reading. Increasingly people are turning to the Internet for more detailed information and trustworthy websites should be recommended to those interested. Mention should be made of local support groups and meetings and contact details of local Alzheimer support organizations. A telephone contact number for information and advice is always appreciated and unlikely to be abused.

Memory aids

The most simple and effective methods of helping patients with cognitive difficulties are the establishment of regular

Table 72.5 Recommendations for telling a diagnosis of dementia to patients and family.

Communication of the diagnosis should ordinarily occur in a *joint meeting with patient and family*
Use *simple language*. Avoid technical jargon that may conceal the truth
Use a graded approach that is patient led and allows the information given to be matched to what the patient wants to know
Allow sufficient time to explain and to answer questions from the patient and family
Assess the patient's and the family 's *understanding* and arrange *follow-up* (to reinforce information provided, clarify misunderstandings and answer questions that are outstanding)
Use the term 'Alzheimer's disease' (or other appropriate medical diagnosis) rather than just dementia and ensure that they understand the sense of both terms
Mellow the bad news with the possibility of therapeutic approaches (not just drugs). Avoid conveying the feeling that 'nothing more can be done'
Make it clear that a reorganized family network can *alleviate burden and maintain quality of life*
Inform the patient about the possibility of taking decisions about his/her future.

Adapted from OPDAL Study Group.[26]

routines, the careful organization of daily activities and the use of environmental cues and external memory aids. None of these require the patient to learn new strategies of thinking or remembering and may therefore be potentially useful in those with even moderately severe dementia. Written aids such as diaries, checklists and carefully positioned notes as reminders are often of benefit and reusable sticky note pads are ideal for sticking in conspicuous places. Labelling or colour coding of switches and doors may sometimes be helpful. A timer or digital alarm watch may act as a reminder to take medication, to attend to cooking or other household tasks or to refer to an appointments diary for guidance as to planned activities. In the kitchen, use of a microwave cooker may avoid food being incinerated in a conventional oven, red warning lights on electrical appliances may help to remind when they are on and use of kettles that whistle may ensure that a planned cup of tea is made and prevent open pans boiling dry. More sophisticated electronic devices and programmable organizers are generally too unfamiliar to the present generation of older people to prove useful, but assistive technology that does not require the person to operate it is attracting much interest. Such telecare can be used to monitor people's activities and trigger an alarm if there is a potential risk, such as flooding from taps left running, gas left on or leaving the house unexpectedly. Sensors and tracking devices can follow people's movements, but raise ethical issues if informed consent cannot be obtained.

Memory training

The idea of cognitive training as a method of improving, retaining or regaining skills is attractive to those worried about memory loss and to relatives who hope that developing problems might be minimized. Recent evidence suggesting that education and continued intellectual activity may reduce the risk of developing AD has further increased interest in this area. Computer-aided brain-training programmes are widely promoted, but so far they seem to meet best the needs of healthy elderly (and not so elderly) people and the worried well.

Experience of formal training programmes designed to improve the cognitive skills of healthy elderly subjects and those with cognitive deficits is limited.[28] Those most likely to gain appear to be well motivated, healthy individuals wishing to conserve their mental faculties as a prophylactic measure. There is little evidence of sustained benefit or generalizability in those with established dementia and regular tests and 'exercises' for the memory can easily become counterproductive. Positive benefits to patients may even be at the cost of increased distress to carers.

Specific approaches have included relaxation techniques, organization of material (e.g. with the use of categorization, associative cues and mnemonics), regular and repeated practice sessions, using spaced retrieval to rehearse information, techniques for improving visual imagery (e.g. peg-word methods, face–name association) and verbal strategies (rhymes, first letter cueing, alphabet searching, etc.). Reactivating therapy, including manual and creative activities, self-management skills and orientation tasks, has been claimed to improve cognitive performance and psychosocial functioning of people with mild dementia. Training in groups with other people with memory impairment or with family members and carers may provide opportunities to harness a wider range of training resources and facilitate expression of mutual support. Another approach is to involve family members in providing the cognitive training at home.

Drug treatments

Memory clinics are now central to the effective prescribing of specific anti-dementia drug treatments. Careful initial assessment and diagnosis are essential before any

pharmacological intervention is considered and the impact of treatment and the indication for its continuing use must be kept under regular review. The size of any drug effect that can be considered worthwhile is open to debate. Statistically significant improvement on psychometric tests does not necessarily equate with meaningful change in quality of life and a noticeable improvement or stabilization is more important than change in test score. Patients and carers tend to be more positive than professionals when assessing apparently small benefits of treatment, with three-quarters believing that halting progression of symptoms of early dementia for about 6 months justifies intervention. Such modest effect would seem comparable to that achieved by the drugs now available

The AChEI drugs have become the mainstay of treatment for AD and may also have benefits in mixed dementia, Parkinson's disease dementia and DLB. They act by inhibiting the breakdown of acetylcholine within the synapse, increasing its availability to muscarinic and nicotinic receptors. In mild to moderate AD, the available AChEI (donepezil, rivastigmine and galantamine) have all been shown to be clinically effective and safe compared with placebo, with improvements in cognition, ADL and overall clinical global impression. There had been some disagreement about their cost-effectiveness but NICE guidance in the UK now supports their use in mild and moderate AD.[29] All AChEIs have qualitatively similar cholinergic adverse effects, including nausea, vomiting, diarrhoea, fatigue and dizziness. These are generally mild and short-lived, resolving despite continued therapy. Caution with the use of AChEIs should be observed in the presence of bradycardia and atrial or ventricular conduction disorders. Muscle cramps, insomnia and nightmares are more common with donepezil and can sometimes be reduced by administering the drug in the morning rather than at night. About 40–60% of AD patients respond to AChEIs. Although similarities appear to be greater than the differences between the available AChEIs, it may be reasonable to consider switching drugs if patients do not tolerate or respond to the first drug used.

Memantine is a non-competitive NMDA (glutamate) receptor antagonist that blocks pathologically elevated glutamate. Glutaminergic overstimulation and consequent calcium overload have been implicated in neurodegeneration and memantine offers neuroprotection, while still allowing physiological receptor activation. The drug is licensed for treatment of moderately severe to severe AD, with patients on memantine in clinical trials showing significantly less deterioration in functional, cognitive and global measures. The emergence of troublesome behavioural symptoms, especially agitation, may also be less, with reduced need for institutionalization and less demands on caregiver time. The addition of memantine to donepezil treatment may show benefit over donepezil alone.

There are many drugs for dementia undergoing research, not only for symptomatic relief but also for disease modification, for example, through interference with amyloid or tau processing in AD and amnestic MCI. Memory clinics continue to provide an ideal setting for patient recruitment and involvement in phase 2 and 3 clinical trials and opportunities for involvement in research should be encouraged.

Over-the-counter medications that have been used to treat mild cognitive impairment and dementia include *Gingko biloba*, vitamin E, folic acid and omega-3 fish oils, but there is no good evidence of efficacy. Often patients and carers will be interested in the effectiveness of complementary and alternative medicine. These non-conventional therapies include herbal medicine, aromatherapy and massage, acupuncture, dietary supplements and melatonin and bright light therapy. The evidence base supporting their use is poor, but there have been few rigorous studies of good scientific design, with adequate patient numbers and using robust outcome measures. Patients and families are attracted by the 'natural' image of these therapies and may feel they have nothing to lose given the inadequacy of conventional treatments. Some will find considerable benefit from them and staff in memory clinics should be able to provide informed information about their safety and local availability, while not necessarily promoting their use.

The memory clinic as part of local dementia services

The World Health Organization and World Psychiatric Association consensus statement[30] on care for elderly people with mental health problems highlighted specific principles that should underpin service development. Good-quality dementia care should be comprehensive, taking into account not just the medical aspects of the problem but also the psychological and social consequences. It should be accessible and user friendly, minimizing obstacles to effective assessment and intervention. It should be responsive, listening to and understanding the problems brought to its attention, and able to act promptly and appropriately. Finally, assessment and care should be individualized, tailored to the needs of the patient and their family.

The consensus document emphasizes that a team approach is essential, not just multidisciplinary but trans-disciplinary, going beyond traditional professional boundaries and providing responsive, coordinated and community-orientated intervention. An effective memory clinic team can be the foundation of a comprehensive dementia service, encouraging early recognition and

specialist referral, providing thorough initial assessment and careful diagnosis and ensuring appropriate high-quality support and care which can be flexibly integrated with other local service providers.

Key points

- Memory clinics offer responsive assessment, diagnosis, treatment and advice for people with memory disorders and for their families. They also act as a focus for professional education and clinical research.
- Most clinics centre on diagnosis and management of mild cognitive impairment and dementia, emphasizing the benefits of early presentation, psychometric assessment, differential diagnosis, appropriate use of drug treatments and psychosocial interventions.
- They have a multidisciplinary approach, with medical, psychology and nursing input and close working relationships with other professionals and dementia services.
- Potential benefits include improved quality of life of patients, reduced carer burden, less hospitalization and possible postponement of need for institutional care.

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CHAPTER 73

Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is the most common form of dementia in older adults.[1] AD symptoms include a loss of memory, impaired judgment and decision-making capacity, a decline in the ability to perform activities of daily living (ADLs), changes in behaviour, mood and personality and increasing dependence on caregivers with expanding degrees of burden and stress.

Alois Alzheimer described the first case in 1906, characterizing a 51-year-old woman who presented with delusions of spousal infidelity, memory and language problems. After her death, using recently developed silver staining techniques, Alzheimer described numerous senile plaques and neurofibrillary tangles characteristic of the disease.[2] For the next 60 years, AD was thought to be an infrequent pre-senile cause of dementia until it was recognized that the clinical symptoms and course and neuropathological findings of disease in individuals younger than 65 years was identical with those found in older adults.

The Alzheimer Association estimates that there are over 5 million people in the USA with AD and that within a generation the number of AD patients will exceed 15 million people.[3] In the USA, AD is the fifth leading cause of death, after cardiovascular disease, cancer, cerebrovascular disease and bronchopulmonary diseases. AD is the third most expensive disease after cardiovascular disease and cancer in terms of total dollars with an annual total (direct and indirect) cost of approximately $172 billion. While the costs of AD increase across the stages of severity, AD patients currently fill nearly half of all nursing home beds. This economic impact will continue to grow as the US population continues to age and the number of AD patients increases. At the time of writing, the cumulative costs of care for people with AD from 2010 to 2050 in the USA will exceed $20 trillion.[3] At present, only symptomatic therapies are available that provide cognitive, functional and behavioural benefits but do not alter the disease course.

Neuropathology

Macroscopically, AD is characterized by cortical atrophy and ventricular dilatation (Figure 73.1a). Volume is most noticeable on coronal sections with shrinkage of medial temporal lobe structures including hippocampus. The characteristic pathological changes in the AD brain are the accumulation of amyloid β-protein in the form of senile plaques and of tau protein in the form of neurofibrillary tangles. Amyloid β-protein (Aβ) is a 39–43 amino acid peptide cleaved from a larger precursor protein [amyloid precursor protein (APP)] found on chromosome 21.[2] Aβ deposits extracellularly as senile plaques that can be visualized by haematoxylin and eosin staining (Figure 73.1b), with the fluorescent dye thioflavin S (Figure 73.1c), by immunohistochemistry using antibodies raised against Aβ epitopes (Figure 73.1d) or with silver impregnation (Figure 73.1e). Amyloid can appear either as loose, non-fibrillar diffuse plaques (Figure 73.1d) or a more compacted, fibrillar form (Figure 73.1b), often with dystrophic neurites coursing through the plaque (neuritic plaque, Figure 73.1e). Cerebral amyloid angiopathy (CAA) is due to the deposition of amyloid in the walls of arteries and arterioles and, less often, capillaries and veins of the central nervous system (Figure 73.1d). The walls of these vessels become very fragile and have a propensity to rupture, leading to superficial cortical haemorrhages. In addition to focal motor and sensory symptoms, repeated haemorrhages can lead to cognitive decline.

Tau protein is a microtubule-associated protein encoded on chromosome 17.[2] Its normal function is to stabilize microtubules and it has numerous sites available for phosphorylation. When hyperphosphorylated, tau forms insoluble filaments that deposit in the cell body of the neuron as a neurofibrillary tangle (NFT) and in the axons and dendrites as neurophil threads (NTs). NFTs in AD are composed primarily of paired helical filaments (two strands of 10 nm diameter filaments that twist around each other

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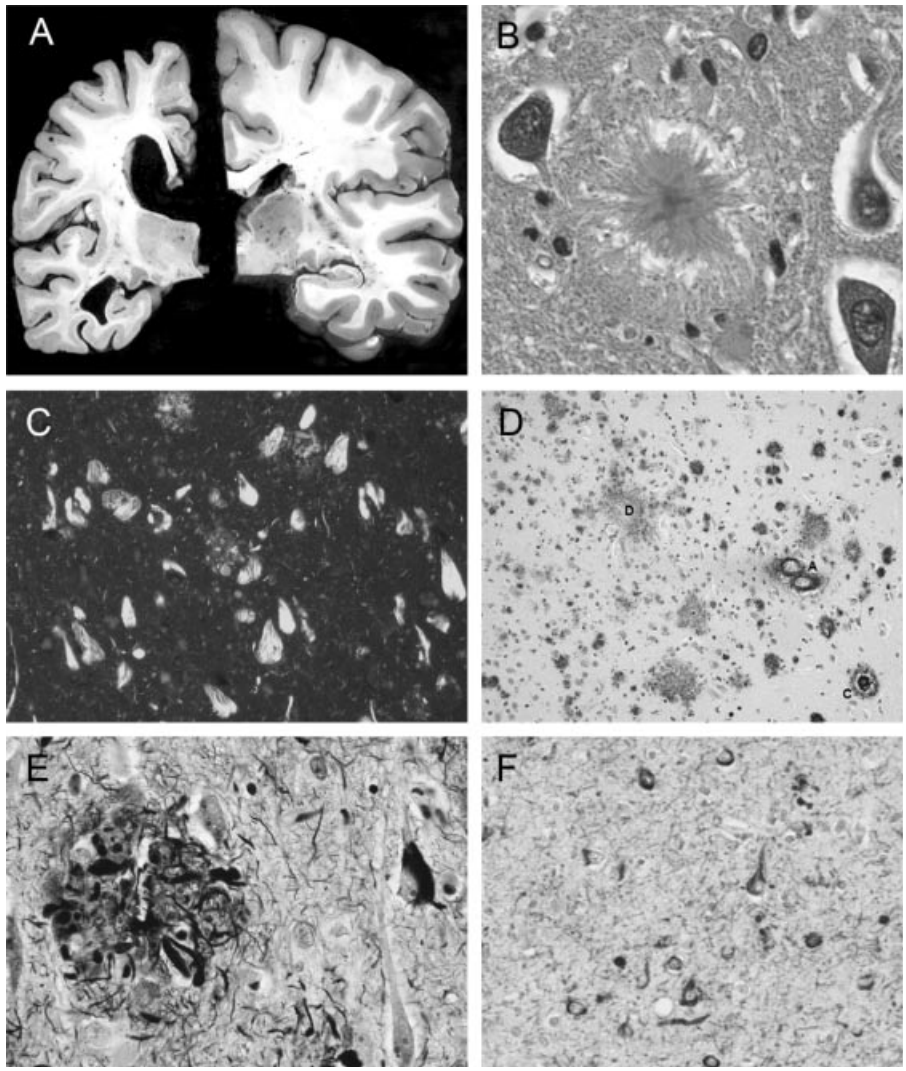

Figure 73.1 The neuropathology of AD. (a) Coronal sections of brain at the level of the hippocampus. On the left is a patient with AD, and on the right is an age-matched individual without cognitive impairment. Note the cortical atrophy and dilatation of the ventricles in the AD patient. (b) Extracellular Aβ senile plaques visualized with haematoxylin and eosin stain. (c) Thioflavin S fluorescent staining of amyloid plaques and neurofibrillary tangles. (d) Immunohistochemistry using Aβ antibodies demonstrating extracellular diffuse and fibrillar amyloid plaques and amyloid deposition in cerebral vessels. (e) Silver impregnation demonstrating fibrillar amyloid with dystrophic neurites and neurofibrillary tangles. (f) Immunohistochemistry using tau antibodies demonstrating neurofibrillary tangles and dystrophic neurites. See plate section for a colour version of these images.

like a helix). NFTs first appear in the hippocampus and entorhinal cortex in the AD brain (Figure 73.1f) and later involve the limbic and neocortex as the severity of dementia worsens. Hyperphosphorylated tau can be visualized by the same methods as amyloid since both proteins undergo transformations to a β-pleated sheet.

Epidemiology and genetics

A number of risk factors have been associated with AD (Table 73.1).[4] Age is clearly the most predictive risk factor. Although cases have been described as early as the third decade, the majority of cases occur after age 65 years. The prevalence of AD doubles each decade from 5% before age 65 years to nearly 50% at age 85 years. After age 85 years, studies are inconclusive as to whether the risk continues to increase; however, pathology characteristic of AD is frequently found in the brains of individuals over 90 years of age. In the oldest old, the course and progression of AD appear to be slower than for those individuals who develop the disease at younger ages. Family history of dementia in first-degree relatives appears to increase the risk of

Table 73.1 Alzheimer risk factors.

Age
Female gender
Family history
Low education
Head injury
Apolipoprotein E ε4 allele
Cardiovascular risk factors: hypertension, diabetes, hyperlipidaemia, homocysteine
Late-life depression
Trisomy 21 (Down syndrome)
Mutations in amyloid precursor protein (APP), presenilin 1 (PS1) or presenilin 2 (PS2)

developing AD. Up to 25% of patients are able to identify a family member with the disease. There is an association between female gender and AD that persists after correction for differences in life expectancy between men and women. The reason for this remains unknown. Earlier epidemiological studies supported a role of postmenopausal estrogen levels; however, the Women's Health Initiative found that estrogen replacement in later life increased rather than decreased the risk for AD.

Low educational attainment may also increase the risk of AD. There is increasing evidence supporting the hypothesis of cognitive reserve, that is, individuals with greater education are better able to stave off the effects of AD pathology in the early stages. Head injury associated with a loss of consciousness has been associated with increased risk of AD. Depression, particularly developing in late life, appears to be a prodromal symptom of AD. There is recent evidence to suggest that the same risk factors for cardiovascular disease may be important contributors to the risk of developing AD, including hypertension, high cholesterol, diabetes and homocysteine.[1,4] Epidemiological studies and chart-reviews have suggested that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of AD; however controlled clinical trials have failed to replicate these results and instead suggest that the use of NSAIDs may increase risks of gastrointestinal, cardiovascular and cerebrovascular disease.

There are also several genetic risk factors. The best characterized risk for late-onset disease is associated with epsilon 4 (ε4) allele of apolipoprotein E (ApoE).[5] ApoE is a cholesterol-carrying protein that may also play a role in handling of Aβ. Three isoforms of ApoE are present, ε2, ε3 and ε4. The ε3 allele is the most common, the ε2 is the least common and the ε4 allele is found in ~20% of the population. The ε4 allele is over-represented in AD, with ~60% of patients carrying at least one ε4 allele. Conversely, the presence of at least one ε2 allele appears to confer some protection. In Caucasians, compared with the ε3/ε3 genotype, individuals with one ε4 allele have a threefold increased risk whereas individuals with two ε4 alleles have a 15-fold increased risk of AD. This relationship holds true across most racial and ethnic groups.[5] The linkage between ApoE and senile plaques suggests that cholesterol homeostasis may play either a direct or indirect role in the pathogenesis. However, because the ApoE genotype is not causative, genetic testing is not recommended as it neither improve diagnostic certainty nor changes the management of the disease. Additional risk genes are being investigated and validated with genome-wide association studies.[6]

Autosomal dominant, early-onset cases of AD are associated with mutations in the amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1).[7] These three mutations appear to increase the production of the 42 amino acid long Aβ protein which has an increased propensity to aggregate. These mutations are rare, but can be suspected in a strong family history of AD with age of onset before 65 years. Even so, the mutations account for a small proportion of AD cases. The real value of the mutations has been in the creation of cell culture lines and transgenic animals that has greatly advanced research efforts. Associated with these genetic risk factors is the virtually certainty of AD developing in individuals with trisomy 21 (Down syndrome) with an additional copy of the region encoding the amyloid precursor protein. By the late 20s, Down syndrome patients begin to accumulate amyloid in their brains and nearly all patients are symptomatic by their mid-50s.[1]

Diagnostic criteria

Although AD can only be definitively diagnosed by autopsy, current clinical criteria permit experienced clinicians to make accurate diagnoses most of the time: 92% or more of the time, an expert clinician's diagnosis is confirmed by autopsy findings. The diagnosis of AD is one of inclusion using standardized clinical criteria: the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)[8] and the National Institute on Ageing – Alzheimer's Association (NIA-AA).[9] The DSM criteria are broader in nature and capture more impaired individuals whereas the NIA-AA criteria apply more rigorous definitions that incorporate new findings regarding the use of biological markers of disease. In general, the current diagnostic criteria are characterized by a two-step procedure with (1) the identification of a dementia syndrome and (2) the exclusion of other aetiologies of a dementia syndrome, using biological and neuroimaging examinations.

The diagnosis can also be based on the criteria of the DSM-IV-TR[8] (Table 73.2). According to the DSM, the essential feature of dementia is impairment in short- and long-term memory, associated with impairment in abstract thinking, impaired judgment, other disturbances of

Table 73.2 DSM-IV criteria for dementia of the Alzheimer type.

The development of multiple cognitive deficits manifested by both
1 Memory impairment (impaired ability to learn new information or to recall previously learned information)
2 One or more of the following cognitive disturbances:
a Aphasia (language disturbance)
b Apraxia (impaired ability to carry our motor activities despite intact motor function)
c Agnosia (failure to recognize or identify objects despite intact sensory function)
d Disturbances in executive functioning (i.e. planning, organizing, sequencing, abstracting)
The cognitive decline causes significant impairment in social or occupational functioning and presents a decline from a previous level of functioning
The course is characterized by gradual onset and continuing cognitive decline
The cognitive deficits above are not caused by any of the following:
1 Other central nervous system conditions that cause progressive deficits in memory and cognition
2 Systemic conditions that are known to cause dementia
3 Substance abuse conditions
The deficits do not occur exclusively during the course of a delirium
The deficits are not better accounted for by another Axis I disorder (depression, schizophrenia)

Adapted from American Psychiatric Association, Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*, 4th edn, American Psychiatric Association, Washington, DC, 1994.

higher cortical function or personality change. Disturbances in these cognitive domains should be severe enough to interfere with social or occupational functioning or disrupt interpersonal relationships with others. An important caveat in the DSM criteria is that the diagnosis cannot be made in the presence of a delirium.[8] There are plans to update the DSM criteria but these are not available at the time of writing.

According to NIA-AA guidelines, the diagnosis is first established by determining the presence of dementia. Dementia is defined as cognitive or behavioural symptoms that (1) interfere with social or occupational functioning, (2) represent a decline from previous level of functioning and (3) are not explained by another disorder. Dementia is established by a combination of a detailed history from the patient and a knowledgeable informant and an objective assessment of cognitive ability. Changes in cognitive ability should involve at least two of the following domains: memory, reasoning and problem solving, visuospatial abilities, language and/or changes in personality, behaviour or social comportment. Once the dementia syndrome is established, the diagnosis of probable AD can be made when the patient has (1) dementia, (2) an insidious onset with gradual progression and (3) worsening of symptoms over time either by observation or report of patient and/or informant. The presentation of deficits can either by amnestic (memory impairment) or non-amnestic (language, visuospatial, executive dysfunction).[9] The diagnosis of AD should not be applied when there is clear evidence of cerebrovascular disease, Lewy body dementia, frontotemporal degeneration or another concurrent neurological, psychiatric or medical condition that can affect condition.[9] If the patient meets criteria for probable AD but has evidence of other disorders that can affect cognition, a mixed dementia syndrome is most likely present.

More importantly, the NIA-AA criteria take into consideration the role of biological markers of disease (biomarkers).[10] Recent advances in biomarker research such as magnetic resonance imaging (MRI), positron emission tomography (PET) scans and cerebrospinal fluid (CSF) biomarkers characterize the underlying pathophysiological processes associated with AD such as evidence of Aβ deposition measured by CSF Aβ levels or PET scans or markers of neuronal injury by CSF tau levels, glucose hypometabolism by PET or cortical atrophy by MRI.[9] Although the use of biomarkers is not advocated for routine clinical use, these tests may increase the diagnostic certainty of AD in difficult cases (Table 73.3).[9]

Evaluation of the AD patient

Clinical evaluation

Knowing that the risk of AD increases with age, older adults are a natural choice for screening for AD. At present, however, there are no formal recommendations for or against dementia screening. The US Preventive Services Task Force (http://www.ahrq.gov/clinic/3rduspstf/dementia/dementrr.pdf) concluded that the evidence is insufficient to recommend for or against routine screening for dementia in older adults. Many of the current brief screening measures such as the Mini-Mental State Examination (MMSE)[11] have good sensitivity but only fair specificity in detecting cognitive impairment and dementia.[12,13] The accuracy of the MMSE depends on a person's age and educational level: using an arbitrary cut-point (typically $\leq$23) may potentially lead to more false-positives among older people with lower educational levels and more false negatives among younger people with higher educational levels.[12]

On the other hand, the early recognition of dementia, in addition to helping make diagnostic and treatment decisions, allows clinicians to anticipate problems the patients may have in understanding and adhering to recommended therapy. Early diagnosis is also beneficial to the patient's caregiver(s) and family member(s) in helping to anticipate

Table 73.3 Probability of AD with biomarkers (NIA-AA criteria).[a]

Diagnostic category	Probability of AD based on biomarkers	Measurements of Aβ (CSF or PIB-PET)	Measurements of neuronal injury or degeneration (CSF tau, FDG-PET, MRI)
Probable AD			
Based on clinical criteria	Not helpful	–/?	–/?
With three levels of evidence based on AD pathology	Intermediate	–/?	++
	Intermediate	+	–/?
	High	+	+
Possible AD			
Based on clinical criteria	Not helpful	–/?	–/?
With evidence based on AD pathology	High (rule out secondary causes)	+	+
Unlikely to be AD	Low	–	–

[a]AD, Alzheimer's disease; Aβ, amyloid beta-protein; CSF, cerebrospinal fluid, PIB, Pittsburgh Compound B (Aβ ligand); PET, positron emission tomography; FDG, [^{18}F]fluorodeoxyglucose; MRI, magnetic resonance imaging;–/?, conflicting or indeterminate; +, positive.
Adapted from McKhann *et al.*[9]

and plan for future problems that may develop as a result of progression of cognitive impairment and for long-term care. Long-term care planning and advanced care decisions are important in all forms of chronic diseases, many of which are treated by neurologists and psychiatrists. Discussions covering these topics early in the course of chronic disease should probably be considered part of the norm, rather than the exception. Organizations such as the American Medical Association, American Geriatrics Society, American Academy of Neurology and American Academy of Family Physicians all recommend that clinicians remain diligent in the early identification of symptoms of AD in their patients.

So who should be evaluated for AD? The Alzheimer Association has published 10 warning signs of symptoms that are most commonly seen in AD (Table 73.4).[3] Although not every individual needs to be extensively worked up, developing a working list of reasons to consider AD as a possible diagnosis is reasonable (Table 73.5). Individuals with identified risk factors warrant further evaluation, as do individuals with memory complaints, with or without functional impairment. Additionally, even if an individual does not complain of memory or cognitive problems, informant complaints (spouses, adult children) should trigger further investigation. Evaluation should include a detailed history from the patient in addition to another source (spouse, caregiver, adult child) to gain insight into how the patient has changed from prior level of function. Historical points should highlight memory impairment (repetition; trouble remembering recent conversations, events, appointments; frequently misplacing items), executive function (deterioration of complex task performance; decreased ability to solve problems; difficulty with calculations; impaired driving), use of alcohol, prescription drugs and over-the-counter medications and the presence of focal neurological symptoms. A complete neurological examination will help to identify other causes of dementia (Table 73.6). Characteristic features of the four most common causes of dementia are given in Table 73.7 to help with differentiation.

Table 73.4 Ten warning signs.

Memory loss
Difficulty in performing familiar tasks
Problems with language
Disorientation with respect to time and place
Poor or decreased judgement
Problems with abstract thought
Misplacing things
Changes in mood or behaviour
Changes in personality
Loss of initiative

Source: Alzheimer's Association.

Cognitive evaluation

Performance-based tools

In terms of assessing cognitive function, the 30-item MMSE test, which takes around 10 min to complete, has frequently been used for initial assessment of AD, and its sensitivity increases if a decline of the score over time is taken into account.[11] The MMSE covers six areas: (1) orientation, (2) registration, (3) attention and calculation, (4) recall, (5) language and (6) ability to copy a figure. However, although the MMSE is quick and easy to administer and can track the

Table 73.5 Indications for evaluating for AD.

Physician observations
Difficulty in learning and retaining new information
Difficulty in performing complex tasks
Impaired reasoning
Problems with orientation and spatial abilities
Language difficulties, particularly word-finding
Behaviour or personality changes
Late-life depression, anxiety or apathy
Previous well-controlled medical conditions now more difficult to manage
Poor medication adherence/compliance
Patient complaints
Memory problems
Work difficulties
New-onset depression, anxiety or apathy
Sleep changes (insomnia, nocturnal movements, unusual dreaming)
Informant complaints
Changes in memory or cognitive abilities
Changes in functional abilities
Changes in mood, personality or behaviour

Table 73.6 Differential diagnosis of dementia.

Neurodegenerative disease
Alzheimer's disease
Dementia with Lewy bodies/Parkinson's disease dementia
Frontotemporal dementia
Huntington's disease
Progressive supranuclear palsy
Corticobasal degeneration
Multiple system atrophy
Wilson's disease
Haemochromatosis/haemosiderosis
Neuronal ceroid lipofuscinosis
Vascular disease
Vascular dementia
Cerebral amyloid angiopathy
CADASIL
Vasculitis
Prion disease
Creutzfeldt–Jacob disease
Gerstmann–Straussler–Scheinker disease
Kuru
Fatal familial insomnia
Hydrocephalus
Demyelinating disorders
Multiple sclerosis
Leukodystrophies
Traumatic brain injury
Metabolic disorders
Hepatic encephalopathy
Hypothyroidism
Storage disorders
Nutritional disorders
Vitamin B_{12} deficiency
Wernicke–Korsakoff syndrome (thiamine)
Mitochondrial disorders
Toxic disorders
Alcoholism
Drugs
Heavy metals
Neoplasia
Primary brain tumours (meningiomas, gliomas)
Metastatic disease
Paraneoplastic syndromes
Infection
HIV/progressive multifocal leukoencephalopathy
Neurosyphilis
Subacute sclerosing panencephalitis
Whipple's disease

overall progression of cognitive decline, it is not considered to be a good test for definitive AD diagnosis,[14] particularly because of its greater emphasis on orientation (10 of 30 points), which is typically not impaired in the earliest stages of dementia. In addition, there are several issues associated with the MMSE, including bias according to age, race, education and socioeconomic status.[15]

Several diagnostic tests are now available for use in primary care as alternatives to the MMSE; these are continually being updated and simplified in order to provide brief, easy to administer and effective diagnostic tools.

The Mini Cognitive Assessment Instrument (Mini-Cog) combines an uncued three-item recall test with a clock-drawing test that serves as a recall distractor; it can be administered in about 3 min and requires no special equipment.[15] The Mini-Cog and the MMSE have similar sensitivity (76 versus 79%) and specificity (89 versus 88%) for dementia, comparable to those achieved using a conventional neuropsychological battery (75% sensitivity, 90% specificity). The Mini-Cog's brevity is a distinct advantage when the goal is to improve recognition of cognitive impairment in primary care, particularly in milder stages of impairment.[15] It has also been suggested that cognitive impairment assessed by the Mini-Cog is a more powerful predictor of impaired ADLs than disease burden in older adults. In addition, the Mini-Cog also has proven good performance in ethnically diverse populations of the USA in which widely used cognitive screens often fail, and is easier to administer to non-English speakers.[15] Furthermore, low educational status, which has been shown to impair

Table 73.7 Characteristic features of the four leading causes of dementia.

Cause of dementia	Symptoms
Alzheimer's disease	Early failure of information storage and new memory creation. Disturbances in attention. May include early language or behavioural disturbances
Frontotemporal dementia	Early behavioural disturbances, particularly social misconduct and eating changes. Early language problems that may be fluent or non-fluent
Lewy body dementia	Early extrapyramidal signs (slowness, stiffness, tremor), visual hallucinations, visuospatial impairment, REM sleep behavioural disorders and fluctuations in attention and concentration
Vascular dementia	Early executive dysfunction usually associated with a focal neurological sign. Presence of vascular lesions in neuroimaging and temporal relationship between focal neurological signs and onset of cognitive symptoms

detection using the MMSE, does not affect the Mini-Cog, which is thus less biased by low educational status and literacy level.

Newer instruments, such as the Montreal Cognitive Assessment (MoCA), are gaining credibility owing to improvements in sensitivity, addressing frontal/executive functioning and decreasing susceptibility to cultural and educational biases.[16] The MoCA is a 10 min cognitive screening tool developed to assist first-line physicians in the detection of MCI. It has high sensitivity and specificity for detecting MCI in those patients who perform within the normal range of the MMSE. Compared with the MMSE, which had a sensitivity of 18% to detect MCI, the MoCA detected 90% of MCI subjects and, in patients with mild AD, the MMSE had a sensitivity of 78%, whereas the MoCA detected 100%.[16]

Informant-based tools

Another key test used in primary care is the AD8 screening interview, which is a brief, sensitive measure that reliably differentiates between individuals with and without dementia by querying memory, orientation, judgment and function.[12,13] The AD8 (Table 73.8) comprises eight Yes/No questions asked of an informant to rate change and takes ~2–3 min for the informant to complete. In the absence of an informant, the AD8 can be directly administered to the patient as a self-rating tool. The AD8 has a sensitivity of 74–80% and a specificity of 80–86%, with excellent ability to discriminate between non-demented older adults and those with mild dementia (92%), and is highly correlated with AD imaging and CSF biomarkers.[13] Use of the AD8 in conjunction with a brief assessment of the participant, such as a word list, could improve the detection of dementia in the primary setting to 97% for dementia and 91% for MCI.[12]

Laboratory Evaluation

In terms of laboratory evaluation for dementia, testing for comorbid medical illnesses that may cause or contribute to onset or progression of dementia is generally recommended.[17] Depression is a common, treatable comorbidity in patients with dementia and should be screened for in older adults. Vitamin B_{12} insufficiency is common in the elderly and vitamin B_{12} levels should be included in routine assessments of the elderly, but screening for other vitamin and nutritional deficiencies is not recommended unless historical information suggests these deficiencies as a clinical possibility. Because of its frequency, hypothyroidism should be screened for in elderly patients. Lastly, unless the patient has some specific risk factor or evidence of prior syphilitic infection or resides in one of the few areas in the USA with high numbers of syphilis cases, screening for the disorder in patients with dementia is generally not justified.[17] This includes collecting spousal history of exposure when applicable.

Genetic testing for patients with suspected dementia is not recommended unless there is clear, generational evidence of an autosomal dominant form of dementia. Even then, genetic counselling is recommended, prior to testing. The routine use of ApoE genotyping in patients with suspected AD is not recommended at present because of cost and because it adds little to the diagnostic accuracy.[17] In patients with clinical diagnoses of AD, the addition of ApoE testing increased the positive predictive value (using the prevalence of AD in this dementia autopsy series) of a diagnosis of AD by ~4% (from 90 to 94%) if an ApoE ε4 allele was present. In patients with a clinical diagnosis of non-AD, the absence of an ApoE ε4 allele increased the negative predictive value by 8% (from 64 to 72%).[18] No other serum or CSF biomarkers have established clinical validity at present and are therefore not recommended, although this is likely to change in the future.

Making the diagnosis

As shown in the algorithm in Figure 73.2, each of the above steps can help to identify the patient-at-risk, establish a likely diagnosis and further treatment recommendations. After establishment of a diagnosis of possible or probable

Table 73.8 The AD8 dementia screening test.

Remember, 'Yes, a change' indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems	**YES, a change**	**NO, no change**	**N/A, don't know**
1. Problems with judgment (e.g. problems making decisions, bad financial decisions, problems with thinking)			
2. Less interest in hobbies/activities			
3. Repeats the same things over and over (questions, stories or statements)			
4. Trouble learning how to use a tool, appliance or gadget (e.g. VCR, computer, microwave, remote control)			
5. Forgets correct month or year			
6. Trouble handling complicated financial affairs (e.g. balancing chequebook, income taxes, paying bills)			
7. Trouble remembering appointments			
8. Daily problems with thinking and/or memory			
TOTAL AD8 SCORE			

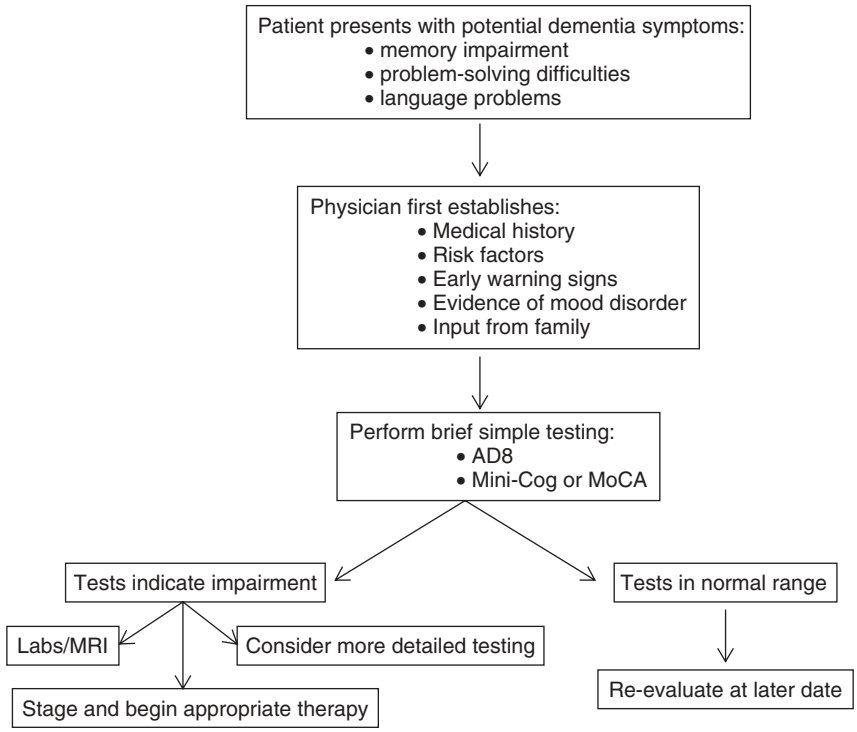

Figure 73.2 Algorithm for the diagnosis of AD in the office setting. This algorithm outlines steps for evaluating older adults for AD or other causes of cognitive impairment. Upon presentation of a patient with dementia-related symptoms elicited by from the patient or caregiver, the physician should first review the medical history to discover the onset, presentation and progression of symptoms, review potential risk factors and evaluate for confounding conditions such as depression. Simple office testing with a performance measure (Mini-Cog or MoCA) and an informant questionnaire (AD8) will enhance the clinician's ability to detect early impairment. If the patient performs in the normal range, periodic reassessment is warranted. If tests indicate cognitive impairment, the clinician should complete the work-up with routine laboratory tests to rule out reversible causes of dementia and neuroimaging. Additionally, the physician can refer to a specialist for more detailed neuropsychological testing. If AD is suspected, the patient should be staged and started on appropriate therapies and referral to community resources.

AD, the patient should be staged to assist in selection of appropriate pharmacotherapies, make referrals to community resources and assist in prognosis (Table 73.9).

There are barriers to the early detection of dementia for the clinician to consider. The first is misidentification of the early stages of dementia by patients and family members as the normal ageing process.[1] Forgetfulness is not a normal part of ageing but is often accepted as an inevitable consequence of growing old. If a patient or family member does not perceive the presence of a memory disorder, they are much less likely to come to medical attention until more advanced stages. A second issue is that social skills are often maintained in the early stages of AD. If a person lives alone, friends and acquaintances may not be able to detect cognitive decline due to lack of exposure. This and the fact of denial and lack of insight by the patient as to the extent of the cognitive problems may also lead physicians to miss early stages of dementia since the patient may not complain and cognitive screening is not part of a routine medical visit in most instances. Even if symptoms are identified by the patient and/or the family, there may be a reluctance to report them due to the social stigma of being diagnosed

Table 73.9 Simple staging scheme for AD.

Stage[a]	Characteristics	Example signs
Mild MMSE 19–27 CDR 0.5 or 1 GDS 3 or 4	• Symptoms are subtle • Self-care capacity, social skills and neurological function remain generally intact • Difficulty with complex tasks; if still working, a decline in job performance • Depression and apathy	• Repeating questions, statements or stories • Misplacing items • Forgetting recent events or conversations • Trouble operating household appliances • Less interest in hobbies
Moderate MMSE 10–18 CDR 2 GDS 5 or 6	• Ability to think, reason, communicate and function deteriorates dramatically • Beginning of behavioural symptoms	• Difficulty in using household appliances • Unable to travel alone • Difficulty in telling time • Restlessness, wandering, insomnia
Severe MMSE 0–9 CDR 3 GDS 7	• Individuals lose capacity for self-care and become completely dependent • Long-term care placement common	• Difficulty in eating, dressing • Incontinence • Cannot answer the telephone • Gait disturbances • Aggression, agitation, irritability

[a]MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; GDS, Global Deterioration Scale.

with AD. The diagnosis can also have consequences for obtaining insurance, employment and driving privileges. These factors can all contribute to delay in diagnosis and should be discussed with the patient and caregiver.

Biomarkers of AD

Cerebrospinal fluid biomarkers

According to the NINCDS–ADRDA guidelines, CSF examination is recommended as an exclusion procedure, largely undertaken to rule out other potentially correctable causes of cognitive decline, such as infection.[9] Since then, research has focused on the validity of AD-specific biomarkers that are reflective of the central pathogenic processes of β-amyloid aggregation and hyperphosphorylation of tau protein. These markers have included β-1–42-amyloid, total tau and phospho-tau: a decrease in the β-1–42-amyloid peptide and an increase in the tau and phospho-tau proteins may be the earliest signs of AD.[13,19] Indeed, both tests produce results with very good sensitivity and specificity. However, at present, these tests are probably not an option owing to patients' reluctance to undergo lumbar puncture and the costs associated with the assays.

Structural brain imaging

Structural brain imaging tests, which include non-contrast computed tomography (CT) or MRI, can evaluate changes consistent with AD and eliminate alternative causes of cognitive impairment.[17] Whenever possible, an MRI scan will provide a greater assessment of regional atrophy and periventricular vascular changes than can be gained from a CT scan. Quantitative MRI and PET amyloid imaging are recent techniques currently being developed to diagnose AD earlier in clinical practice. Within an AD diagnostic framework, the ideal role of structural brain imaging tests is to increase the specificity of clinical criteria.[17]

Functional brain imaging

PET scanning appears to have promise for use as an adjunct to clinical diagnosis, but further prospective studies with PET are needed to establish the value that it brings to diagnosis over and above a competent clinical diagnosis. One of the largest series of dementia cases that underwent PET scans and also had autopsy confirmation yielded a sensitivity of 93% and a specificity of 63%.[20] PET diagnostic accuracy increases with more advanced stages of dementia (87.2% for MMSE score >20 and 100% for MMSE score <20).[21] There are somewhat specific patterns of brain hypometabolism for each dementia subtype. In AD, hypometabolism is noted in the posterior temporoparietal cortices.[21] Fluorodeoxyglucose (FDG) PET may also be superior to MRI measures of hippocampal atrophy because changes in cerebral glucose metabolism antedate the onset of memory decline, whereas the MRI hippocampal changes may not reflect early disease.

Management

Disclosing the diagnosis

Disclosure of the diagnosis of AD to the patient and family may be difficult and consideration of the emotional

responses should be taken into account. A family conference may be the most appropriate setting and the physician should be prepared to answer questions from the patient and family regarding the certainty of the diagnosis, the prognosis and implications for care. Recent research suggests that there is little long-term psychological effect of disclosing an AD diagnosis and both caregiver and patient self-ratings of depression and anxiety may be alleviated by having a frank, honest discussion about the disease.[22]

Setting treatment goals

Setting realistic treatment goals is critical to increasing patient and caregiver adherence. Because the currently available medications are symptomatic, it is important that the patient and family do not leave the physician's office under the impression that they will 'get better' by taking the medications. Although some patients do show improvement in different cognitive areas, the goal of current therapy for AD is to stabilize the patient for a period of time or to progress at a slower rate. As each patient has unique living and social situations, the clinician can work with the family to set expectations and discuss the limitations of current therapy.

Therefore, treatment goals should be discussed at the time of diagnosis. The first is to establish realistic expectations of treatment and review the course and complications of the disease. Goals should be set to (1) maintain quality of life, (2) maximize function and ADLs, (3) stabilize cognition, (4) treat mood and behavioural problems and (5) reduce caregiver burden.[1] Other discussion topics should include advanced directives, financial planning, referral to community resources, driving, durable power of attorney and discussion of long-term care planning. Addressing issues early in the diagnosis will empower the patient and caregiver to participate in the decision-making process.

Currently available management options for dementia

Although current pharmacological and behavioural interventions do not prevent eventual disease progression, they arguably lead to improvements in understanding, self-efficacy and quality of life for the patient and family. Recognizing dementia in its early phase may provide substantial benefits, including financial, medical and legal planning. It will also enable patients, their families and their caregivers to understand and deal better with the nature of the condition and subsequent changes in behaviour, allow caregivers to become familiar with appropriate support and social services and help maintain patients' functioning at the highest level possible.[23]

Managing mood disorders and behaviour problems

Traditionally, cognitive function has been the main focus of interest in treatment and research for people with dementia. It is becoming increasingly recognized, however, that non-cognitive symptoms are those that are most disturbing to families and caregivers and may seriously impact not only the patient's wellbeing, but also the family's, caregivers' and providers' approaches to managing the patient.[24] The most common symptoms are agitation, aggression, mood disorders/behavioural disturbance, apathy, depression, psychosis and hallucinations, with sexual disinhibition, elation/euphoria, appetite and eating disturbances and abnormal vocalizations occurring less frequently.[1,24] These have been grouped together under the umbrella term 'behavioural and psychological symptoms of dementia' by the International Psychogeriatric Association.[25] As the disease progresses, these symptoms become predominant problems and impose an enormous toll both emotionally and financially. They are also a common reason for institutionalization of people with dementia and they increase the burden and stress of caregivers.

Non-pharmacological interventions

Non-pharmacological interventions are recommended as the most appropriate initial strategy for managing inappropriate behaviours in dementia for the following reasons: (1) they address the psychosocial/environmental underlying reason for the behaviour and (2) they avoid the limitations of pharmacological interventions, namely adverse side effects, drug–drug interactions and limited efficacy.[24,26] Increased involvement of caregivers often has a secondary benefit of providing overburdened caregivers with an opportunity to receive support, information and skills. Further, environmental factors (e.g. confusing or noisy surroundings) or interpersonal factors (e.g. arguing with the patient) are often the primary triggers of behavioural problems. Attention to these factors through non-pharmacological approaches can be effective in alleviating or preventing behavioural problems in individuals with dementia. Unfortunately, in practice, pharmacological approaches involving psychotropic or sedative medications are often used as the first-line treatment, despite the modest evidence of efficacy from clinical trials where high placebo response rates are frequently seen, rather than first attempting a non-pharmacological approach.

An increasing number of non-pharmacological therapies are now available for people with dementia (Table 73.10). It should be noted that there are several areas of overlap between these therapies, hence each approach is rarely

Table 73.10 Non-pharmacological approaches and principles to behavioural therapies.

Standard therapies
Behavioural therapy
Reality orientation
Validation therapy
Reminiscence therapy
Alternative therapies
Art therapy
Music therapy
Activity therapy
Dance therapy
Aromatherapy
Bright-light therapy
Multisensory approaches
Brief psychotherapies
Cognitive behavioural therapies
Interpersonal therapy
Reducing behavioural symptoms
Provide the patient with a predictable routine (e.g. exercise, meals and bedtime should be routine and punctual)
Allow the patient to dress in his or her own clothing and keep possessions
Ask permission before touching patient or their belongings
Explain instructions to the patient in simple language
Simplify tasks; break up a complex task into steps and provide instruction for each step
Use distraction and redirection of activities to divert the patient's attention
Ensure that comorbid conditions are optimally treated
Provide a safe environment (e.g. no sharp-edged furniture, no throw rugs)
Equip doors and gates with safety locks
Install grab bars by the toilet and in the shower
Use calendars, clocks, labels and newspapers for orientation to time
Use colour-coded or graphic labels as cues for orientation in the home environment
Use lighting to reduce confusion and restlessness at night
Avoid glare from windows and mirrors, noise from a television and household clutter
Reduce excess stimulation and outings to crowded places
Consider using a day-care programme

used in isolation. It is therefore important for a clinician to have some knowledge of a number of these approaches, enabling a combination of treatments tailored to the individual requirements of the patient to be offered.[24] Therapy is now directed towards person-centred forms of care and, using this approach, greater attempts are made to understand the individual's experience of dementia and to employ strategies to improve quality of life.[26]

Pharmacological interventions

There are currently no means of reversing the pathological processes of AD. Therefore, the specific goals of therapy are to preserve cognitive and functional ability and to minimize behavioural disturbances and slow disease progression with maintenance of patients' and caregivers' quality of life. Early initiation of cholinesterase inhibitors (ChEIs) may temporarily stabilize or delay disease progression, which provides obvious desirable benefits for patients and caregivers. Studies have shown that both caregiver burden and overall cost are reduced by anticholinesterase therapy.[27] Beneficial response to a ChEI (i.e. stabilization or delayed deterioration of cognitive or behavioural problems) may be assessed from the physician's global assessment of the patient, the primary caregiver's report, a neuropsychological assessment or mental status questionnaire or evidence of behavioural or functional changes.

Five drugs have been approved for treating AD: four ChEIs approved for mild to moderate disease, one of which is also approved for severe AD, and a glutamate *N*-methyl-D-aspartate (NMDA) antagonist approved for moderate to severe disease (Table 73.11).

Mild to moderate disease

ChEIs have been the cornerstone of treatment for patients with mild to moderate AD for over a decade. Four ChEIs are currently available: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl). These agents raise acetylcholine levels in the brain by inhibiting acetylcholinesterase, they tend to stabilize memory during the first year of treatment and they may slow the subsequent decline.

The systematic reviews and randomized controlled trials carried out to date, all of which involved at least 6 months of follow-up, found a significant difference that favoured the ChEI compared with placebo, ranging from 2.12 to 3.4 points on the ADAS-Cog scale. Donepezil 5 and 10 mg per day doses have been associated with significant improvements of–2.01 and–2.80 points, respectively, on the ADAS-Cog scale at 24 weeks, compared with placebo; donepezil 10 mg per day was also associated with a significant 1.84-point improvement over placebo on the MMSE at 52 weeks.[28] In addition to their effects on cognition, these agents have also demonstrated beneficial effects on measures of behaviour, ADLs and global patient function.

A meta-analysis which analyzed clinical results from 29 randomized, placebo-controlled trials of patients with mild to moderate AD found that ChEI therapy was associated with significant modest benefits in terms of neuropsychiatric and functional outcomes.[29] Current guidelines acknowledge that preventing or delaying further loss

Table 73.11 Pharmacological therapies for AD.

Drug	Approved indication	Suggested dosage	Side effects	Additional notes/caution
Cholinesterase inhibitors				
Tacrine (Cognex)	Mild to moderate AD	Four times daily dosing regimen	Poor tolerability and significant hepatotoxicity	Second-line agent owing to pharmacological characteristics and side effects Causes elevation of liver enzyme levels in 40% of patients; therefore, biweekly liver tests are necessary during dosage escalations and every 3 months thereafter
Donepezil (Aricept)	Mild to severe AD	Once daily, beginning with 5 mg per day, which can be increased to 10 mg per day (maximum dosage) after 4 weeks. Also available as an oral disintegrating tablet	Adverse effects are mild and include nausea, vomiting and diarrhoea	Gastrointestinal-related adverse effects can be reduced if the medication is taken with food Some patients exhibit an initial increase in agitation, which subsides after the first few weeks of therapy
Rivastigmine (Exelon)	Mild to moderate AD	*Oral* Twice daily, beginning with 1.5 mg twice daily. Also available as a 2 mg ml^{-1} oral solution *Transdermal patch* Once daily, 4.6 or 9.5 mg The target dose is 9.5 mg per 24 h patch (a 10 cm^2 patch) and requires a simple one-step dose titration to the therapeutic dose	Adverse effects include nausea, vomiting, diarrhoea, weight loss, headaches, abdominal pain, fatigue, anxiety and agitation. Gastrointestinal-related adverse effects less prominent with patch	Higher dosages are more efficacious than lower dosages No laboratory monitoring is required
Galantamine (Razadyne)	Mild to moderate AD	Twice daily, beginning with 4 mg twice daily After 4 weeks, the dosage is increased to 8 mg twice daily to a maximum of 12 mg twice daily Available in an extended-release formulation (8, 16 and 24 mg) that can be taken once daily. Also available as a 4 mg ml^{-1} oral solution	Most common side effects are nausea, vomiting and diarrhoea	Gastrointestinal-related adverse effects can be minimized by titrating the dosage gradually and taking the medication with meals
NMDA antagonists				
Memantine (Namenda)	Moderate to severe AD	Twice daily, beginning with 5 mg twice daily, increasing the dose to 10 mg twice daily over 3 weeks	Adverse effects include fatigue, pain, hypertension, headache, constipation, vomiting, back pain, somnolence	Moderate to severe AD may respond better with memantine–donepezil combination than with donepezil alone

of ADL function is an important goal of AD therapy and significant preservation of ADL function has been observed with donepezil, galantamine and rivastigmine compared with placebo. Patients treated with ChEIs and/or memantine may also experience behavioural benefits in terms of reduced severity of existing behavioural disturbances and fewer new behavioural symptoms, usually agitation/aggression and irritability, whereas depression, apathy and anxiety do not respond.[27] In an open-label study using the neuropsychiatric inventory (NPI), donepezil was shown to reduce significantly the severity of neuropsychiatric symptoms in patients with mild to moderate AD (mean total score: 25.4 versus 15.2 at baseline versus 12 weeks; $p<0.001$). With the exception of elation, all domains of the NPI were significantly improved from baseline. During the subsequent 12 week period, in which patients either continued with donepezil therapy or switched to placebo, these improvements were sustained with donepezil therapy, whereas patients receiving placebo experienced significant worsening in NPI scores.[30]

ChEIs have also been shown to reduce AD caregiver burden: in patients with moderate to severe AD, donepezil treatment for 24 weeks significantly reduced caregiver time spent assisting patients with basic and instrumental ADLs (–52 min per day; $p<0.005$). A small study has demonstrated that rivastigmine treatment reduces caregiver time spent assisting with ADLs (up to 690 h over 2 years).

Long-term treatment with ChEIs may also decrease the risk for nursing home placement.[31] A retrospective analysis of a large US medical claims database showed that over a 27 month follow-up period, more patients who were not treated with ChEIs were placed in nursing homes (11.0%) than those who received either rivastigmine (3.7%) or donepezil (4.4%).[32] These studies suggest that ChEIs enable patients to live longer in community settings, with associated personal, social and economic benefits.

Moderate-to-severe disease

Memantine is approved for the treatment of moderate to severe AD, based on a study in which patients with moderate to severe AD who received 20 mg memantine monotherapy showed less decline in cognition and function, while maintaining good tolerability, after 6 months than those who received placebo.[32] The ChEI donepezil has also recently been approved for use in severe AD. Donepezil has also been associated with reduced burden for caregivers of patients with moderate to severe AD. In one trial, the caregivers of patients receiving donepezil therapy reported spending almost 1 h less per day on assisting with ADLs than the caregivers of placebo-treated patients.[33]

There is also evidence that combination therapy with ChEIs plus memantine improves clinical and functional outcomes compared with placebo or ChEIs alone.[34]

Medical foods

Medical foods represent a new alternative to be considered for integration into a comprehensive therapeutic regimen for patients with AD. They comprise a US Food and Drug Administration (FDA)-regulated product defined by Congress as part of the Orphan Drug Act. Such products currently being marketed in the USA for the management of dementia include Axona (caprylic triglyceride) and CerefolinNAC. Other medical foods are also being developed, such as Souvenaid.

Axona has been developed for the clinical dietary management of the metabolic processes associated with mild to moderate AD. It is a formulation of caprylic triglyceride, a medium-chain triglyceride that is metabolized to ketone bodies, predominantly β-hydroxybutyrate (BHB). BHB is a common metabolic substrate that is normally produced by the body for neurons in starvation states where glucose is less available.[35] A double-blind crossover study conducted in patients with AD or MCI demonstrated that Axona therapy was associated with significant improvements in ADAS-Cog; however, the effect was only seen in patients who were ApoE ε4 non-carriers. Similar results were reported in a 90 day randomized, placebo-controlled study in patients with mild to moderate AD.[35] Gastrointestinal disturbances were the most commonly occurring adverse events in the clinical trials. In the 90 day study, one-quarter of patients taking Axona experienced diarrhoea compared with 14% in the placebo group. Gastrointestinal side effects are reportedly reduced by administration of Axona with a meal or mixing it with a drink.

CerefolinNAC, which contains L-methylfolate, methylcobalamin and *N*-acetylcysteine, is indicated for the distinct nutritional requirements of individuals under a physician's treatment for neurovascular oxidative stress and/or hyperhomocysteinaemia, including patients diagnosed with AD. The efficacy of its ingredients regarding cognitive performance has been assessed in various trials.[36]

Souvenaid combines omega-3 fatty acids, choline, uridine monophosphate and a mixture of antioxidants and B vitamins. In a randomized controlled trial involving more than 200 patients with very mild AD, Souvenaid was well tolerated and improved memory, compared with placebo.[37]

Behavioural management

Behavioural management with psychotropic agents

Pharmacological interventions are necessary when non-pharmacological strategies fail to reduce behavioural symptoms sufficiently. Although ChEIs and memantine may improve these symptoms, if behavioural disturbances persist despite their use then a psychotropic agent may be necessary.

If a psychotropic agent is needed, the rule 'start low and go slow, but go' (i.e. the agent should be initiated

in a low dosage that should be increased slowly) should be followed and the patient should be closely monitored for side effects and adverse events. The dosage should be increased until an adequate response occurs or side effects emerge; potential drug interactions should also be considered. After behavioural disturbances have been controlled for 4–6 months, the dosage of psychotropic agent should be reduced periodically to determine whether continued pharmacotherapy is required. The choice of psychopharmacological agent is determined by specific target symptoms; some behaviours, such as wandering and pacing, are not amenable to drug therapy.

Atypical antipsychotics

Atypical antipsychotic drugs have been commonly used off-label in clinical practice for the treatment of serious dementia-associated agitation and aggression, although they have not been approved by the FDA for such use. The FDA analysis of the 17 registration trials across six antipsychotic drugs indicated a statistically significantly elevated risk of death in drug-treated patients (either heart-related or from infections) that was 1.6 times greater than in placebo-treated patients. These findings should be taken seriously by clinicians in assessing the potential risks and benefits of treatment in a generally frail population and in advising family members about treatment options. In general, psychotropic agents should be used only when non-pharmacological approaches have failed to control serious behavioural disruption adequately within 5–7 days.[38] A useful rule of thumb is that a behaviour needs to addressed pharmacologically when that behaviour interferes with patient care, patient safety or the safety of another individual. At all times, the prescriber in conjunction with the patient and caregiver should address the benefit–risk balance in this patient population. Other concerns regarding the use of antipsychotics involve a higher incidence of side effects in elderly patients, including sedation, falls and extrapyramidal signs, with recommendations that their use in this patient population should be carefully monitored.

Additional options for pharmacotherapy include trazodone, carbamazepine and valproate, although the data are inconclusive. Tricyclic antidepressants, antihistamines and benzodiazepines should be generally avoided in this population. Selective serotonin reuptake inhibitors appear to have efficacy for the treatment of agitation in patients with AD. Studies have demonstrated benefits for agitation with citalopram, compared with placebo, and similar efficacy, compared with risperidone.[39]

Future therapies

ChEIs and memantine are symptomatic therapies that help maintain neuronal function but do not have a significant impact on the underlying disease process. Their benefits are mild and treatments that modify the disease course are urgently needed. AD is currently thought to be a complex, multifactorial syndrome, unlikely to arise from a single causal factor; instead, a number of related biological alterations are thought to contribute to its pathogenesis. This may explain why the currently available drugs, developed according to the classic drug discovery paradigm of 'one molecule one target', have turned out to be palliative. In the light of this, drug combinations that can act at different levels of the neurotoxic cascade offer new avenues towards ameliorating the symptoms of AD.

Conclusion

The rising prevalence of AD suggests that all health providers will have an increasingly important role in the diagnosis and subsequent management of disease. A key factor in the optimal treatment and outcome of AD is the timely and accurate diagnosis of dementia, with diagnostic tools that can identify dementia early and precisely. There has been an unprecedented growth of scientific knowledge about AD. The distinctive and reliable biomarkers that are now available through structural brain imaging with MRI, PET and CSF analyses, along with a clearer definition of the clinical profile of amnestic disorders that occur early in the course of disease, have made it possible to identify AD with high accuracy, even in its early stages. New criteria for AD diagnosis are being proposed that may allow the detection of not only symptomatic disease but also prodromal states. Of the newly available diagnostic tools for use by primary care physicians, the Mini-Cog, MoCA and AD8 may be particularly useful as brief, easy to administer and effective diagnostic assessments that can be used in everyday clinical practice.

The treatment of AD consists of both pharmacological and non-pharmacological interventions. Non-pharmacological interventions are recommended as the most appropriate initial strategy for managing inappropriate behaviours in dementia. An increasing number of non-pharmacological therapies are now available. Given that there are currently no means of reversing the pathological processes of AD, the primary objectives of pharmacological interventions are to preserve cognitive and functional ability, minimize behavioural disturbances and slow disease progression. To date, five drugs have been approved for treating AD: four ChEIs, which have been the cornerstone of treatment for patients with mild to moderate AD for over a decade, and an NMDA antagonist. On occasions, it may be necessary to prescribe a psychotropic agent, with atypical antipsychotic agents commonly used off-label for serious dementia-associated agitation and aggression, and antidepressants, having been prescribed for patients with AD who also suffer from depression. Future therapies may include amyloid-modifying drugs,

acetylcholine receptor agonists, mitochondrial inhibitors and tau-based and neuroprotective approaches.

Key points

- AD is the most common form of dementia.
- Both pharmacological and behaviour therapies may improve the outcomes in AD.
- Plaques are formed by amyloid β-protein.
- Phosphorylated tau produces neurofibrillary tangles.

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CHAPTER 74

Mild cognitive impairment

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Introduction

The concept of mild cognitive impairment (MCI) as an intermediate state between normal cognition and dementia entered into the vernacular of geriatric medicine in the past 15–30 years. What this chapter may add to our understanding is that it is a relatively precise clinical diagnosis and a useful research tool. More often than not, the clinical diagnosis of MCI may have be applied to patients who are either normal or who have dementia. Although this misclassification may be a disservice to the diagnosis of MCI, the bigger disservice is to the patient. Geriatricians need to use the diagnosis appropriately for patient care, understand the treatment limitations, apply appropriate management strategies and embrace the research opportunities presented by this construct.

History

Mild cognitive impairment as a term was introduced into the literature in 1988 by Reisberg *et al*.,[1] but referred to a severity index of stage 3 as identified on the Global Deterioration Scale. Another instrument, the Clinical Dementia Rating Scale, sought to identify very early dementia given the possibility of identifying disease early and intervening as soon as possible.[2] By 1999, MCI had been proposed as a prodromal condition for Alzheimer's disease (AD) with the focus on memory as a chief clinical complaint for incipient disease.[3]

It was evident by the turn of the decade that not all forms of MCI evolved into AD. However, the general construct served most clinicians well enough. The difficulty was then, and still is today, that all too often MCI is used to soften a diagnosis of what should really be dementia. In 2004, Winblad *et al*.[4] sought to expand and revise the criteria.[5] From the symposium concerned, the criteria now used by the National Institute on Aging-Sponsored Alzheimer Disease Centers Program Uniform Data Set and the Alzheimer Disease Neuroimaging Initiative (ADNI)[6] have helped us design protocols to improve our understanding of the dementing process. The clinical phenotypes now include amnestic MCI (aMCI) and non-amnestic MCI (naMCI) with the subtypes of single- and multiple-domain classifications (Figure 74.1).

While specific changes in cognition are frequently observed in normal ageing, there is increasing evidence that some forms of cognitive impairment are recognizable as an early manifestation of dementia.[3] MCI is a heterogeneous state and there remains controversy over aspects of the construct. However, the utility of this paradigm is the recognition that dementia is not a dichotomous state and therefore refining our understanding of the layers of transition will improve the understanding of cognitive decline and ultimately benefit patients. Appropriate diagnosis lets us address our patients' needs with the best available therapies, be they drug or non-drug interventions.

In general, our shortcomings in approaching patients with cognitive decline have been to avoid a diagnosis and delay our interventions. The reasons are multiple, although taking the time to make a diagnosis means that much more time will be needed to explain the diagnosis and take action. Any assault on our independence with special concern regarding the loss of driving privileges plays poorly to the American mindset. We live in a land where our first right of passage is our driver's license and where all roads lead to the shopping mall. We do not live in walking communities and the last thing we give up is our driver's license. There have also been financial disincentives in the past when clinicians used a psychiatric code to define cognitive disease although MCI and the dementing syndromes can b now e classified with ICD-9 medical codes.

Although no symptomatic or disease-modifying drug therapies are available for MCI, there is much that can be done. The domains of cognition, function and behaviour define this population and where they reside in the spectrum of disease. Their preserved abilities can also

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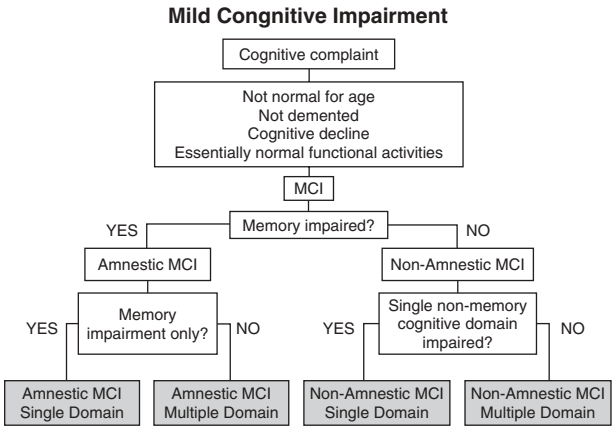

Figure 74.1 MCI flowchart. Reprinted from Petersen[5] with permission.

serve as markers for how the disease is progressing and how well they are living within a defined environment. Even without a drug treatment of MCI, understanding the environment that surrounds every one of these patients and how they function within their universe is most important. Overlearned behaviours and an environment that limit or prohibit excess disabilities should be stressed even for patients with MCI. Much can be done and running towards a diagnosis is better than running away from it.

Cognitive impairment, be it MCI or dementia, can still be defined by the capacities that are preserved and the capacities that are lost. This is where the issue of driving comes into play, but the concept applies to all kinds of tasks and opportunities. We counsel that a diagnosis is not an all-or-nothing phenomenon and many individuals with MCI or even early dementia sit on advisory boards to provide a patient voice in understanding better the needs of the patient. Unfortunately, explaining these concepts and what is both retained and what is lost takes time, especially for the primary care provider.

As our understanding of disease advances, the triad of cognition, function and behaviour not only defines the type of care that may be appropriate but also contributes to our understanding of where the best site of care might be. Our ability to address the environment early in the care of patients with MCI or other age-dependent deficiencies may improve the quality of life for our parents, avoid common pitfalls and provide for more cost-effective and successful management of the being, not just the disease they may have. A goal set by the Alzheimer's Association back in 1987 was to create an environment where a person can function with *minimal* failure and *maximal* use of retained abilities. There is even more opportunity today to create this success with earlier diagnosis and earlier intervention.

Our earliest work in the Mayo Alzheimer's Disease Research Center taught us that even normal individuals change as they get older. Not only does reaction time slow but on measures of Verbal IQ and measures of Performance IQ, the things we do day in and day out are better preserved.[7–9] In all of our attempts at providing care to the elderly, these are the principles that shaped us early and continue to play out in the advice we give out every day. Overlearned behaviours, repetitive tasks and rehearsed activities make it easy and comfortable for us to go about the routines of the day. The things we are confronted with that take an element of problem solving become all the more difficult as we age.

In addition, the concept of MCI plays extremely well as we design hypothesis-driven research; be it with regard to clinical markers, psychological assessment, neuroimaging, biomarkers or drug and non-drug interventions.[10] This is perhaps equally important as the clinical diagnosis and has generated research opportunities worldwide. The construct of MCI has been incorporated into research on ageing from multiple perspectives, including clinical research, epidemiology, neuroimaging, mechanisms of disease, clinical trials and caregiving.[10]

Definitions and terminology

Mild cognitive impairment (MCI) refers to cognitive impairment that does not meet the criteria for dementia. Various researchers have proposed several criteria for and subtypes of MCI.[3,11,12] These criteria and subtypes differ somewhat, although there is considerable overlap. The Mayo criteria are the ones most commonly applied in the literature:[13]

- memory complaint, preferably corroborated by an informant
- memory impairment documented according to appropriate reference values
- essentially normal performance in non-memory cognitive domains
- generally preserved activities of daily living
- not demented.

It is important to emphasize that these remain clinical criteria. Considerable judgment is involved in making the distinction between impairments that are normal for the elderly population and, at the other extreme, that do not represent dementia. However, it should be noted that this is the manner in which we apply criteria for dementia and AD also. Each follows a construct, has a literature base and serves the patient best when appropriately applied.

MCI is heterogeneous in terms of clinical presentation, aetiology, prognosis and prevalence.[12,14,15] In recognition of the narrower scope of the original Mayo criteria and others that relied heavily on memory problems, the concept was expanded. The intention of this was to broaden the scope and extend the emphasis of detection of other dementias in their prodromal stages.[5,13,16] A useful classification criteria separates MCI into amnestic and non-amnestic groups and

further into single and multiple domains. The amnestic type of MCI is generally thought to represent prodromal AD.[17] Other subclasses may have different underlying mechanisms of cognitive impairment and may be associated with other non-AD disease processes [e.g. vascular dementia, frontotemporal dementia (FTD) or dementia with Lewy bodies (DLB)], but there is limited pathological evidence for this paradigm.[18]

The term MCI, without qualification, was traditionally and is still often used to refer to the amnestic type; however, using MCI without qualification is not the current state of affairs. This chapter includes the current breakdown into the various subtypes.

Single-domain amnestic MCI

Single-domain amnestic MCI (aMCI) refers to those individuals with significantly impaired memory who do not meet criteria for dementia. The criteria outlined above were initially developed to define MCI in general, but subsequently have been understood to identify only this type.[3,13]

Memory impairments that qualify for MCI are generally represented by defects that are 1.0–1.5 standard deviations (SDs) or more below age-corrected norms. Although this seems straightforward, different tests of memory likely have different sensitivity and specificity and norms are not available for all populations.[14]

Multiple-domain amnestic MCI

Many individuals with aMCI complain only of memory loss; however, they may have additional subtle impairments in other cognitive domains, for example, executive function, that are revealed with careful neuropsychological testing.[16,19–21] Some would interpret the latter finding as excluding patients from this subtype of MCI according to the criteria listed above.[14] This highlights the operational difficulties with the application of the criteria and was a primary reason for expanding the diagnostic categories to include single- and multiple-domain impairment.[5] Such persons may manifest subtle problems with activities of daily living, but they do not meet criteria for a formal diagnosis of dementia.[15] The multiple domains are, by definition, only slightly impaired (i.e. less than 0.5–1 SD below age- and education-matched normal subjects).

aMCI is often thought of as a precursor to AD.[17] Although memory performances are often similar in patients with aMCI and AD, the addition of impairments in multiple cognitive domains are also prominent in patients with AD.[3] Suffice it to say, the greater the extent of additional non-memory domains the smaller the distinction between MCI and AD becomes and the greater is the risk of conversion to dementia.

Often these individuals progress to meet criteria for AD or vascular dementia; in a minority of cases, the cognitive profile may simply reflect normal ageing.[15] The prognostic utility of the multiple-domain form of MCI remains unclear as some studies have identified this as the highest risk category for conversion to dementia whereas others have exposed instability, with some individuals returning to baseline level of function over time.[16,22,23] It may represent a progression of impairment from the memory domain alone to multiple domain involvement on the way to dementia.

Single-domain non-amnestic MCI

The concept of single-domain non-amnestic MCI (naMCI) is similar to that for aMCI, except that this form of MCI is characterized by a relatively isolated impairment in a single non-memory domain, such as executive functioning, language or visual spatial skills.[15] Depending upon the domain, individuals with this subtype of MCI may progress to other syndromes, such as FTD, including primary progressive aphasia, DLB, progressive supranuclear palsy (PSP) or even corticobasalganglionic syndrome (CBS). Individuals within this group appear to be at less of a risk for conversion to dementia, although supporting evidence is limited by the operationalization of MCI diagnosis.[18,24] Uncommonly, AD may present without a memory impairment initially, so naMCI can occasionally be a prodromal state of AD.

Multiple-domain non-amnestic MCI

As with aMCI, patients who meet this criterion are affected in multiple domains with a relative sparing of memory problems. The substrate of multiple-domain naMCI is felt to be that of degenerative disorders associated with tau, TAR DNA binding protein (TDP-43) and α-synuclein such as FTD and DLB.[25,26]

Although these criteria were developed as an ontological concept relating early changes in specific cognitive domains to those areas most commonly affected in the disorders, that is, memory problems and AD, there remains a significant amount of crossover between groups.[18] Additionally, in certain disorders, such as behavioural variant FTD, cognitive complaints are often preceded by significant alterations in behaviour and comportment. Hence some have proposed the concept of mild behavioural impairment as a similar paradigm to recognize an additional group with increased risk of dementia.[27]

Related terminology

There are a multitude of loosely related terms that have been used to describe constructs that are similar to or perhaps even the same as MCI, for example, incipient

dementia, isolated memory impairment, dementia prodrome, minimal AD, predementia AD, prodromal AD and early AD.[3,12,13,15,28,29] In a glossary of these and other terms that describe cognitive impairment in elderly people without dementia, most of these definitions do not fully overlap with the definition of MCI.[30]

The concept of MCI perhaps reflects most closely the idea of 'cognitive impairment, no dementia' (CIND).[31] However, in contrast to the definition for the amnestic form of MCI, CIND relies less heavily on the presence of prominent memory deficits and includes in its definition the presence of a functional disability. It is a more inclusive definition than MCI and includes static encephalopathies, as is reflected by its higher prevalence.

'Age-associated memory impairment' (AAMI) and 'age-associated cognitive decline' (AACD) are also widely used and fairly well-known terms. However, these terms differ from MCI in that they were originally devised to define normal age-associated memory and cognitive changes in older adults as referenced to young normal adult individuals.[3,32,33] AACD was developed as a way of defining better the cognitive changes in elderly compared with age-adjusted norms. AACD has more recently been recognized as identifying a state of impairment similar to MCI.[34] In MCI, memory impairments are referenced to age-adjusted norms and require a decline from a previous level of functioning.

Studies of 'preclinical AD' should be distinguished from studies of MCI.[35] In MCI studies, patients meet cognitive criteria for diagnosis and are then followed prospectively to assess for conversion to AD. As we move forward with our understanding of disease, we expect presymptomatic cases to be described and defined by biomarker data.

Some investigators challenge the inclusion of intact activities of daily living as a criterion and have suggested further refining the concept of subjective cognitive complaint.[36-38] These and other judgments likely differ between assessors and account for some of the conflicting results in studies of this disorder. It is also important to note that an essential component of the diagnosis of MCI is based on the clinical history and should not rest on psychometric testing or a hesitancy to diagnose a dementia appropriately.

Case examples

The clinical presentation of a patient with MCI typically involves a cognitive complaint. Patients or family members commonly report difficulties with 'short-term memory' (by which they mean recent memory) but detailed history-taking should also ask about symptoms in other cognitive domains. Motor, neuropsychiatric, autonomic and sleep symptoms also may be present and should be elicited specifically during the initial evaluation. However, the field has expanded and the differential now includes a variety of subcategories including naMCI. Two examples may help in understand the current differentiations. Potential interventions as practiced by providers who wish to intervene early are included.

70-year-old man with amnestic MCI

This patient has a memory complaint and lacks other cognitive difficulties.

A 70-year-old right-handed male presents with a 2 year history of memory complaints. His wife mentions that he tends to misplace items, forget conversations and repeat himself. He maintains all activities of daily living and admits to having trouble with his memory. Although he finishes tasks with accuracy, he takes a slightly longer time to finish activities such as balancing the chequebook. He scores 34/38 on the Kokmen Short Test of Mental Status,[39] losing all four points on recall. His general neurological examination is within normal limits. Formal neuropsychological testing shows impairment only in the memory domain, with difficulties in delayed verbal recall. Performance on tests of attention-executive functioning, visuospatial skills and language is in the above-average range. Screening laboratory tests did not reveal a reversible cause for his cognitive difficulties. His brain magnetic resonance imaging (MRI) scan is significant for mild bilateral hippocampal atrophy.

Discussions were undertaken early on regarding the patient's cognitive complaints. He had preserved insight and was well aware that there was a problem. The discussion was 'hopeful' although his clinician was very clear that a diagnosis could already be established and that progression to a dementing syndrome still carried a strong likelihood. No drug therapy was offered and his type 2 diabetes had been well managed. An additional review of his medications revealed the use of oxybutynin for an overactive bladder and it was suggested that this drug be discontinued because of its anticholinergic burden. The family was most appreciative of this suggestion and had questioned whether the drug had provided any benefit in the first place. This discussion also provided the clinician with the opportunity to introduce the potential use of a cholinesterase inhibitor should the patient go on to manifest additional disease.

The opportunity also presented itself with regard to managing the environment of care. There had been some talk of moving to a warmer climate now that the patient was retired. They had vacationed in the previous two winters in a retirement community and enjoyed the experience. However, the patient had shown some reluctance in making a permanent move as he had misplaced the golf cart on more than one occasion. The conversation therefore turned to the most appropriate time to move and where to move. Patients with cognitive difficulties do best with stable and predictable environments. Learning becomes more difficult

and the recommendation was either to move as soon as possible or not to move at all. In this way, the patient would have either the greatest opportunity to adjust to his new surroundings or benefit from the continuing, predictable and overlearned environment already surrounding him.

75-year-old woman with non-amnestic MCI

This patient's cognitive impairment is affecting attention-executive functioning and the visuospatial domain.

A 75-year-old right-handed female presents with a 2 year history of progressive cognitive difficulties. Her daughter reports that she does not multitask or make decisions as well as she did after her husband's death 10 years ago. She also takes longer to complete the laundry and finds it challenging to fix holiday meals. Otherwise, she maintains all activities of daily living independently and continues to drive to the grocery store. Both she and her daughter reported no problems with memory. On examination, she scores 33/38 on the Kokmen Short Test of Mental Status. Although she lost two points on learning, two points on calculation and one point on construction, she was able to state all four words on the delayed recall task. Her general neurological examination was significant for mild bradyphrenia, bradykinesia and hypomimia. Formal neurological testing showed impairment in attention-executive functioning and visuospatial skills, with above-average performance on measurements that tested the memory and language domains. Screening laboratory tests did not reveal a reversible cause for her cognitive difficulties. Her brain MRI scan also was unremarkable, without any evidence of cerebral or hippocampal atrophy.

The patient's daughter lives out-of-state and no close relatives or friends could be counted on for support. Power of attorney for healthcare had been established shortly after the husband's death and this was an opportunity to discuss additional advance directives. The patient had no plans for a living will but had talked extensively with the daughter about her husband's death. She did not want to go on a ventilator as he did after his heart attack and lived like a 'vegetable' after his subsequent stroke. They were both in agreement that it would be best if she moved closer to her daughter and with the clinician's support it was recommended that they do this sooner rather than later.

The daughter sought out local support and was a close friend of a social worker who worked at the neighbourhood hospital. As the mother was moving to a bigger city, there were many opportunities (none of which included living with the daughter). Both mother and daughter looked at a number of options together and, with advice provided by the social worker, chose a large campus that was essentially a continuing care retirement community. The rationale was that the mother would be able to live quite independently, although she planned to give up driving. Should her condition deteriorate, the campus had graduated programmes to attend to her needs. However, the entire campus maintained a unified philosophy, was easy to navigate and seemed to understand that patients should be left to function on their own whenever they had preserved abilities to do so. It was unlikely that the patient would ever leave the campus as a large, skilled nursing care facility was also part of the package.

Why does it matter?

If we wait for functional decline to define dementia, it may be too late to treat the underlying disease process.[40] Moreover, since functional decline is in the definition of dementia, it is best to work with a construct that would allow intervention sooner rather than later. With this theoretical framework, many studies have been conducted to investigate the utility and prognostic outcome of the diagnoses.[40]

Numerous investigations worldwide have used these criteria as an infrastructure for estimating the frequency of MCI and its subtypes.[14,18,20,41] Both prospective[18,42] and retrospective studies[36] have helped to define the subtleties of the diagnosis. A major factor in determining outcome depends on the source of the patient being studied. The closer one is to a community sample, the lower are the annual rates of progression (6–10%).[43] With referral-based studies, such as those that come from sampling a memory disorders clinic or AD centre, the progression rates rise to 10–15% per year, particularly for AD.[44] These differences reflect the probability of having an underlying disorder such as MCI when a participant or concerned family member seeks treatment at a referral clinic. The same phenomenon occurs at dementia 'screening' clinics that advertise their services and claim diagnostic rates approaching 50%. This is in the face of baseline incidence rates of dementia and AD of 1–2% per year.[3] Published rates of progression are summarized in Table 74.1.

Epidemiology

The Mayo Clinic Study of Aging was designed as a population-based study in Olmsted County, MN, USA, involving a random sample of nearly 3000 participants aged 70–89 years who were non-demented and cognitively normal or who had MCI at entry.[45,46] The prevalence of MCI from this study is estimated at ~15% of the non-demented population, with a 2:1 ratio of aMCI to naMCI. The most common putative cause is degenerative and this cause predominates to a greater extent for aMCI than for naMCI. There is evidence that these rates tend to hold up throughout the world at about 14–18% for individuals aged 70 years and older.[10] The overall progression rate for all MCI

Table 74.1 Rates of progression.

Source	Study location	No. of participants	Participant age range (years)	Reported rate of progression	Annual crude progression rate (%)[a]
Solfrizzi *et al.* (2004)[86]	Italy	1524	≥65	3.8/100 person-years	3.8
Busse *et al.* (2006)[18]	Leipzig, Germany	863	≥75	44% per 4.3 years	10.2
Tschanz *et al.* (2006)[87]	Cache County, UT, USA	3266	≥65	46% per 3 years	15.3
Fischer *et al.* (2007)[43]	Austria	476	75–76	33.9% per 30 months	13.6
Ravaglia *et al.* (2008)[88]	Italy	937	≥65	14% per 1 year	14
Farias *et al.* (2009)[89]	California	111	>60	3% per 1 year[b]	3.0
Petersen *et al.* (2010)[46]	Rochester, MN, USA	1969	70–89	7.5% per 1 year	7.5

[a]Annual crude progression rates (%) are reported in the data or estimated from the crude rates.
[b]In the Farias study, the rate of progression for the clinic cohort is reported as 13% per 1 year.

Table 74.2 Prevalence studies.

Source	Study location[a]	No. of participants	Participant age range (years)	Prevalence of MCI (%)
Unverzagt *et al.* (2001)[90]	Indianapolis, IN, USA	2212	≥65	23.4
Hanninen *et al.* (2002)[91]	Finland	806	60–76	5.3
Lopez *et al.* (2003)[42]	CHS	1690	≥75	22
Ganguli *et al.* (2004)[14]	MoVIES	1248	≥65	3.2
Busse *et al.* (2006)[18]	Leipzig, Germany	980	75–79	19.3
Das *et al.* (2007)[92]	India	745	≥50	14.9
Di Carlo *et al.* (2007)[93]	Italy	2830	65–84	16.1
Fischer *et al.* (2007)[43]	Austria	697	75	24.3
Manly *et al.* (2008)[94]	Manhattan, NY, USA	2364	≥65	21.8
Palmer *et al.* (2008)[95]	Kungsholmen, Stockholm, Sweden	379	75–95	11.1
Plassman *et al.* (2008)[96]	ADAMS	856	≥71	22.2
Roberts *et al.* (2008)[45]	Rochester, MN, USA	1969	70–89	14.8

[a]Abbreviations: ADAMS, Aging, Demographics and Memory Study; MoVIES, Monongahela Valley Independent Elders Survey; CHS, Cardiovascular Health Study.

by consensus is 8.5% and by concordance 9.4%. Published prevalence studies are summarized in Table 74.2.

Neuropathology

There are not many neuropathological studies to shed light on the clinical syndrome as patients survive much further into their disease course before succumbing to death and potential autopsy. The Religious Orders Study followed up a group of nuns and priests for many years and achieved high autopsy rates. The study reported that ~60% of the participants with MCI have neuropathological evidence of AD, but that vascular disease also accounts for significant pathology.[47] Other studies have implicated the importance and the findings of neurofibrillary tangle density to account for the symptoms of MCI.[48]

Two additional studies come from our own investigations. We evaluated participants who died while their clinical classification was MCI and found that most had a low probability of having the neuropathological features of AD at that point in time.[49] A second study observed participants who had been previously diagnosed with MCI and had progressed to dementia and characterized these participants as having diagnostic pathology. This study indicated that, while most of the participants with aMCI developed AD, another sizeable group (20–30%) developed another type of dementing disorder.[50] These studies remain in contrast to opinions that the discoverable pathology of MCI, albeit more advanced MCI, is only AD.[51,52]

Approaching the patient and their caregiver

The clinical history remains the mainstay in making a diagnosis of MCI. It is all about what insight the patient

maintains in understanding their memory deficit. However, obtaining a history from both the patient and an informant may provide further support that a cognitive decline does exist.[53] Questions about cognition should address all major domains, including memory, attention-executive functioning, visuospatial skills and language. Common memory symptoms include the tendency for frequent repetition or forgetfulness of recent events.

Patients with attention-executive functioning impairment may have problems in making decisions, planning activities and multitasking. Visuospatial difficulties may be elicited by asking about a tendency to get lost while driving or an inability to track the lines on a page while reading. Word-finding difficulty, paraphasias, and/or anomia may indicate language dysfunction. The history taking should also focus on functional status, including the ability to drive, manage finances and maintain basic activities of daily living. Possible neuropsychiatric, motor and sleep issues should be addressed, as the presence of these symptoms may suggest a possible aetiology of an MCI subtype.

Language difficulties, disinhibition or socially inappropriate behaviour may be seen in those with FTD; REM sleep behaviour disorder (RBD), characterized by a tendency to act out dreams, has been associated with DLB. A past medical history may reveal cerebrovascular disease, seizures, head trauma, systemic cancer or infections that may be contributing to the cognitive impairment.

The time course of symptoms is also important. A gradual, insidious progression of symptoms may suggest a degenerative cause, whereas a more acute onset may indicate a vascular, inflammatory or infectious aetiology. Loss of concentration may be a presenting symptom, but it is more often associated with depression than with cognitive impairment. Good screening tests for depression are readily available and the PHQ-9 has found its way into many office practices.[29] The PHQ-9 is the nine-item depression scale of the Patient Health Questionnaire. It is a powerful tool for assisting primary care clinicians in diagnosing depression and also selecting and monitoring treatment.

The primary care clinician and/or office staff should discuss with the patient the reasons for completing the questionnaire and how to fill it out. It can be done by intact patients or used as a survey instrument and done by just about anyone. After the patient has completed the PHQ-9 questionnaire, it is simply scored. There are two components of the PHQ-9: (1) assessing symptoms and functional impairment to make a tentative depression diagnosis and (2) deriving a severity score to help select and monitor treatment. It also responds to treatment initiatives with clinically validated changes in the patient's response.

The PHQ-9 is based directly on the diagnostic criteria for major depressive disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). It is replacing the Geriatric Depression Scale in many situations and will soon become the depression scale on the nursing home Minimum Data Set 3.0. It offers better sensitivity than older tests and can be used across a greater age range. It is also used in many of the research protocols in evaluating mood in dementia states. No evaluation of a cognitive complaint is complete without an evaluation for depression.

After a history has been obtained that will also evaluate the impact of decline, a general neurological examination should be performed. Any practitioner with appropriate experience can do the examination. Although the examination may be normal, abnormalities could suggest a potential aetiology for the cognitive deficits. Parkinsonism may be seen with DLB and also other neurodegenerative disorders, motor neuron signs may be associated with FTD and focal deficit consistent with a specific vascular distribution may suggest a vascular cause for the cognitive impairment.

In addition to a general neurological examination, a screening mental status examination, such as the Mini-Mental State Examination (MMSE), 3 MS, VA–St Louis University Mental Status Examination or Kokmen Short Test of Mental Status, should be administered.[39,54,55] Severity of symptoms may be determined using assessments such as the Clinical Dementia Rating scale (CDR).[2] A formal neuropsychological battery also can be performed and should include tests that sufficiently challenge a patient in each cognitive domain.

After adjusting for age and education, scores below 1.0–1.5 SDs below the mean typically indicate cognitive impairment on neuropsychological testing.[56,57] Learning and recall tasks may differentiate subjects with MCI from those experiencing normal ageing. On measures of general cognitive function such as the MMSE and full-scale IQ, the individual with MCI performs more similarly to a normal elderly subject, while memory function on delayed verbal recall (Logical Memory II) and non-verbal delayed recall (Visual Reproductions II) more closely resembles mild AD.[3]

Although the screening mental status examination and neuropsychological battery may be useful, it is important to remember that these tests may not be sensitive to cognitive impairment. Individuals may score within the 'normal' range, particularly those with high premorbid intellectual functioning. Despite normal scores, these patients may have MCI, if the clinician determines that there has been a change from baseline functioning. In these circumstances, it is usually best to follow these patients clinically, with repeat evaluations at regular intervals.

Laboratory tests used in the evaluation of dementia may identify medical issues that could affect cognitive function.[58] Basic laboratory tests that look for reversible causes of cognitive impairment include a complete blood count, basic metabolic panel, thyroid function tests, vitamin B_{12} levels and folate levels. Neuroimaging with MRI or computed tomography (CT) of the brain is also

recommended to look for any structural abnormalities that may be contributing to symptoms.

Information from the history, screening mental status examination, neuropsychological testing and ancillary studies should be used to determine if cognitive function is changing, normal or impaired. Functional status can be obtained from the individual, the informant or both. If the patient has experienced cognitive decline but has maintained most daily activities, then that individual can be given an MCI diagnosis. Once an individual has been diagnosed as having MCI, the clinician can determine the MCI subtype based on which cognitive domains are impaired. From this determination, the MCI subtype can be made. If memory impairment is present, then the individual has an aMCI subtype. I f memory is preserved but evidence of decline is seen in other cognitive domains, then the subtype is naMCI.

After establishing the subtype as aMCI or naMCI, the next step is to determine if one or more cognitive domains are affected. If memory is the only domain affected, then the subtype would be single-domain aMCI; if at least one other cognitive domain is also affected, then the subtype would be an multiple-domain aMCI. If the impairment was isolated to one of the non-memory domains, then the subtype would be single-domain naMCI; if two or more non-memory domains were affected, then the subtype would be multiple-domain naMCI. Again, function must be essentially preserved to differentiate multiple-domain MCI from dementia.

The goal of such subtyping in clinical practice is to describe accurately the individual's clinical syndrome and to determine the possible aetiology of the patient's symptoms. Using the history, examination and ancillary data, the clinician can begin to deduce whether the cause of impairment is degenerative, vascular, psychiatric or secondary to concomitant medical disorders. Such deductions may assist in providing treatment options for each patient.

Natural progression of disease and outcomes

Since MCI is considered to be a transitional state between normal ageing and dementia, the aetiologies for dementia theoretically could be applied to MCI. While the construct has yet to be validated, aMCI due to a degenerative aetiology is thought to progress most likely to AD – an assertion that has been endorsed in a practice parameter from the American Academy of Neurology.[13]

Although a diagnosis of MCI places an individual at higher risk for developing dementia, it does not indicate that the patient necessarily will progress to a dementia state. Although the majority of the MCI subjects in one large prospective trial progressed to AD at a rate of 7–10% per year, a small percentage of these individuals improved to normal.[18] Others have been known to remain clinically stable for many years and may not develop dementia.[59] These potential outcomes should be discussed with patients and their families after a diagnosis of MCI has been made.

Genetic contributions

aMCI due to a degenerative cause most likely has similar features to clinically probable AD, with risk factors such as age, hypertension and diabetes.[60-62] Apolipoprotein ε4 (ApoE4) carrier status is a recognized genetic risk factor for the development of AD,[63] but its value for detecting progression to cognitive impairment is less clear. It has been a consistent predictor but has not found a useful way into clinical practice.

Some studies have suggested that ApoE4 carrier status may have assist in predicting those more likely to convert from MCI to AD,[64-66] and a synergistic effect with depression has been seen in cognitively normal individuals at risk for developing MCI. ApoE4 carrier status also may be associated both with hippocampal atrophy in MCI subjects and with higher rates of cognitive decline in cognitively normal adults.[67,68] However, others have shown that ApoE4 carrier status itself has not been demonstrated to predict cognitive decline or conversion to AD,[69] and its routine use is not recommended;[70] the diagnosis of MCI is made clinically.

Treatment

Early detection of cognitive decline theoretically may lead to the implementation of therapies that slow the progression of impairment. However, there currently is no FDA-approved treatment intervention for MCI. Since the aetiologies of MCI can be heterogeneous, medications targeting a neurodegenerative cause theoretically would be different from those targeting cognitive impairment due to vascular, psychiatric or other medical disorders. Clinical trials nevertheless have focused on the aMCI subtype, with the goal of slowing the progression to AD.

A number of studies have targeted medications used in the symptomatic treatment of clinically probable AD. These medications have included three of the cholinesterase inhibitors – donepezil, galantamine and rivastigmine.[71–73] Additionally, vitamin E and rofecoxib have been studied,[71,74] as both oxidative damage and inflammation have been implicated in the pathophysiology of AD.[75-78] Unfortunately, none of these interventions have shown a significant reduction in conversion rates of aMCI to AD, ranging from 6 to 17% in the medication arms versus from 4 to 21% with placebo. However, one study did find that donepezil reduced the progression risk for 12 months in those with aMCI – an effect that persisted up to 24 months in ApoE4 carriers.[71]

Despite the results of clinical trial data, these studies do support the construct of MCI as a transitional state between normal cognition and AD. The overall progression rates for MCI in these studies ranged from 5 to 16%, which are higher than the incidence rate for AD in the general population.[3,71] These rates suggest that patients who meet MCI criteria are at a higher risk for developing AD. Since not all of those with MCI develop AD pathology, more accurate identification of these subjects is essential. Incorporating potential predictive biomarkers in clinical trials may assist in testing compounds that target the underlying disease process of AD.[79]

A variety of non-drug interventions have also been tried on this population. Not surprisingly, cognitive training has been the most studied. The environment of care has been addressed and lifestyle management has been included. Interventions range from individualized therapy to group programmes that additionally address activity planning, self-assertiveness training, relaxation techniques, stress management, use of external memory aids and motor exercise. Multicomponent interventions seem to benefit activities of daily living, mood and memory performance. A standardized cognitive training manual has been proposed in addition to further studies utilizing larger sample sizes and more robust experimental designs.[80-82]

Advance care planning

Patients and families should be aware that those who have aMCI due to a degenerative cause may have a 10–15% chance of developing AD; however, it also should be noted that MCI is heterogeneous, with a number of potential outcomes.[59] Although some patients may not develop dementia, the label of 'mild cognitive impairment' nevertheless may lead to psychological consequences, such as a feeling of uncertainty or concerns of becoming burdensome to others.[83] Neuropsychiatric symptoms such as depression, anxiety, apathy and/or irritability may also be seen in those with MCI and may be associated with progression to AD.[84]

As identified in the two case examples above, encouraging patients and their families and caregivers to consider decisions about advance directives, future planning and finances is essential, especially if the cognitive impairment is thought to be due to a degenerative cause. Although definitive data are limited, patients should be encouraged to follow a heart-healthy diet and to remain active physically, intellectually and socially. Participation in a cognitive rehabilitation programme may also be useful in MCI subjects, with improvements in activities of daily living, mood and memory. Although these modifications may improve their overall quality of life, there has not been enough research to support a decreased progression from aMCI to AD.

Future directions

The MCI construct has become useful in the early detection of those at risk for developing dementia. Given the heterogeneity of the MCI subtypes and their potential aetiologies, identifying these individuals with more accuracy is essential. One area of future research is in developing a predictive profile for these patients. With aMCI, for example, a combination of ApoE4 genotypes, cerebrospinal fluid (CSF) biomarkers and neuroimaging findings on MRI, fluorodeoxyglucose positron emission tomography (FDG-PET) and Pittsburgh Compound B (PiB)-PET may identify those who are more likely to progress to AD, as opposed to some other pathology.

The Alzheimer's Disease Neuroimaging Initiative (ADNI), which began in October 2004, has gathered and analysed thousands of brain scans, genetic profiles and biomarkers in blood and CSF. Although the original goal was to define biomarkers for use in clinical trials to determine the best way to measure treatment effects of AD, it has been expanded to using biomarkers to identify AD at a predementia stage. There are over 800 participants comprised of 200 with AD, 400 with MCI (AD) and 200 with normal cognition. The next step is to scan and analyze the brains of people with early mild cognitive impairment (eMCI).

The scope of ongoing research has been expanded to enrol participants at an earlier stage of MCI, when symptoms are milder. Studies include PET, FDG-PET (which measures glucose metabolism in the brain), PET using a radioactive compound (PiB) that measures brain β-amyloid and structural MRI. Biomarkers in CSF are revealing other changes that could identify which patients with MCI will develop AD. Levels of β-amyloid and tau in CSF may also be predictive.

Longitudinal studies also need to be performed on the various MCI subtypes. Whereas there has been a plethora of research on aMCI and its association with AD, there is a lack of information on the outcomes of naMCI; some research has even suggested that both aMCI and naMCI subtypes may progress to AD.[43] Similarly to AD, other neurodegenerative disorders such as DLB and FTD may pass through an MCI state, although this presumption has not yet been validated. There is even ongoing work to help define stages of illness that precede MCI, such as subjective cognitive impairment (SCI).[85]

Finally, neuropsychological tests that are more sensitive in detecting cognitive impairment should be developed, as they may assist in identifying those with early MCI. In those with high intellectual premorbid functioning, scores on screening mental status examinations and formal neuropsychological batteries may be within normal limits. Nevertheless, these patients may still be diagnosed with MCI, especially if the clinician believes that there has been

a decline from the individual's baseline cognition. More research is starting to be performed in this population of patients.

Being able to identify patients at risk for developing dementia is essential for clinical trials. Possible disease-modifying agents for AD currently are at various stages of investigation, including modulators of amyloid processing, active and passive immunization strategies and monoclonal antibodies. More accurate identification of MCI individuals may structure enrolment procedures and endpoints in future studies and hopefully will lead to better outcomes in subsequent treatment trials.

Conclusion

The MCI construct implies a intermediate state between normal cognition and dementia. Individuals with MCI have (a) a subjective cognitive complaint that is usually corroborated by an informant, (b) preserved general cognitive functioning, (c) impairment in one or more of the cognitive domains (memory, attention-executive function, visuospatial skills and/or language) and (d) essentially normal activities of daily living. Once the diagnosis of MCI has been made, the specific subtype can be determined, with aMCI referring to the presence of memory impairment and naMCI referring to the presence of impairment in one or more of the other domains with relative preservation of memory.

MCI remains a clinical diagnosis, aided by a thorough history, neurological examination, screening mental status examination and formal neuropsychological testing. Although an individual with high premorbid intellectual functioning may score within the normal range on bedside and formal testing, that patient may still be considered to have MCI based on the judgement of the clinician. Since there is subjectivity in the clinical diagnosis, creating an operational definition for clinical trials has been a challenge. In addition, a number of aetiologies can be associated with MCI, including degenerative and vascular processes, psychiatric causes and comorbid medical conditions.

The most researched subtype has been aMCI. Thought to be a risk factor for AD, the aMCI subtype has been associated with increased rates of progression to AD compared with the general population. A great deal of research has been performed to determine factors that may predict this progression, with more recent studies combining data on clinical, genetic, neuroimaging and surrogate biomarkers. While further studies clearly need to be performed in order to refine the MCI construct and its potential aetiologies, the ultimate goal is to use this construct as a tool in developing treatments that will potentially prevent or delay the progression of dementia. If a profile of neuroimaging and surrogate biomarkers can be used in conjunction with an MCI diagnosis and if that profile can indicate accurately which patients with MCI are most at risk for progressing to AD, then perhaps there is the potential for moving the AD diagnosis to an earlier stage and subsequently treating these patients even before they develop dementia.

Key points

- MCI is a relatively precise clinical diagnosis.
- Multiple-domain amnestic MCI has an increased likelihood of progressing to AD.
- Medications have failed to decrease conversion rates of MCI to dementia.
- Multicomponent interventions improve mood, memory performance and activities of daily living.

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CHAPTER 75

Vascular dementia

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Introduction

Considered in the past as the second most common cause of acquired dementia after neurodegenerative pathologies in the elderly, it is now recognized that cerebrovascular disease is associated with a heterogeneous group of cognitive impairment from mild cognitive impairment to dementia and/or mood disorders that share a presumed vascular cause and that extend well beyond the traditional concept of multi-infarct dementia (Figure 75.1).[1] There is also agreement that cerebrovascular disease contributes to cognitive impairment in neurodegenerative dementias, defining the so-called mixed dementia. The concept of vascular depression describing depression occurring in later life associated with vascular risk factors or white matter lesions is still debated.[2]

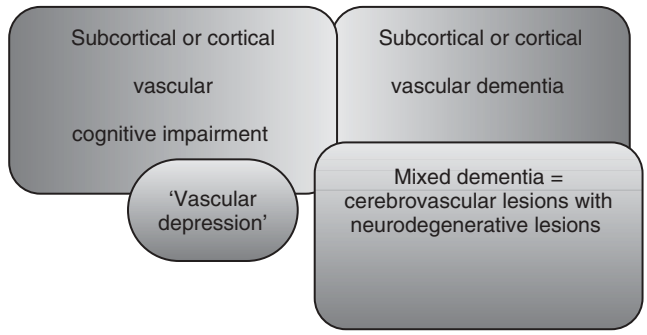

Figure 75.1 The broad spectrum of cognitive consequences of cerebrovascular disease.

Definition, physiopathology and classification

Vascular cognitive impairment (VCI), with or without dementia, is a multifactorial disorder related to a wide variety of lesions and causes. To take into account the heterogeneity of clinical, neuropsychological and radiological appearances related to the different vascular mechanisms and brain lesions, VCI could be defined as the loss of cognitive function resulting from ischaemic, hypoperfusive or haemorrhagic brain lesions due to cerebrovascular disease. Classification is based on the onset of cognitive impairment (acute or subacute), the location, type, number and size of brain lesions (cortical or subcortical, single or multiple stroke, lacuna), the mechanisms (ischaemic or haemorrhagic), the size of involved vessels (small or large vessels) and origin of vascular disease (atherosclerosis, arteriosclerosis, inflammation or genetic) (Table 75.1).[3]

The main cause of vascular dementia (VD) is related to vascular changes due to risk factors such as hypertension, diabetes and dyslipidaemia. Very rare causes due to inflammatory pathologies have been described, mainly in young people. Genetic forms of VD have been identified such as the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) associated with a notch 3 family gene on chromosome 19.[4] Clinical manifestations include migraine with aura, recurrent ischaemic stroke, depression and progressive cognitive decline with early-onset VD. Other hereditary VDs are characterized by amyloid angiopathy leading to cerebral haemorrhages and dementia as in the amyloidosis-Dutch type, the BRI2 gene-related dementia (British and Danish type) and amyloidosis-Icelandic type due to variant cystatin C.[5] Sporadic cerebral amyloid angiopathy cases have also been described.[6]

A growing body of evidence suggests that cerebral white matter magnetic resonance imaging (MRI) grade abnormalities described as leukoaraiosis may also contribute to cognitive impairment. Periventricular and/or subcortical lesions are often seen with increasing age in demented and non-demented elderly people and seemed to be correlated with dysexecutive symptoms[7,8] and dementia.[9]

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 75.1 Classification of vascular cognitive impairment aetiologies.

	Vessels involved	
	Large vessel disease	**Small vessel disease**
Location of lesions	Multiple cortical infarcts Single strategic stroke	Periventricular white matter lesions Thalamic infarct or lacuna in basal ganglia or in frontal white matter
Mechanisms and aetiologies	Ischaemia Extracerebral embolism: • Large artery atherosclerosis (carotid, . . .) • Cardiac embolism, atrial fibrillation, . . .	Ischaemia: • Arteriolosclerosis • Hypertensive arteriopathy • Inflammatory disease: primary vasculitis (giant cell arteritis, primary angiitis of CNS, periarteritis nodosa, . . .) and vasculitis secondary to collagen vascular diseases, Behçet disease and other systemic conditions • CADASIL Haemorrhage: • Hypertension • Amyloid angiopathies, . . .
Other haemorrhages	Traumatic subdural haematoma Subarachnoid haemorrhage	
Hypoperfusive	Diffuse anoxic encephalopathy (cardiac arrest)	

In CADASIL, cognitive decline and mood disturbances have been associated with extensive white matter hyperintensities on baseline MRI, clinically silent brain infarction, cerebral microhaemorrhages and changes in microstructure on diffusion imaging.[10] Cortical atrophy has also been implicated in cognitive impairment in VD.[11]

Numerous neuropathological studies have pointed out concomitant Alzheimer's lesions such as neurofibrillary tangles and neuritic plaques in VD or concomitant vascular lesions in Alzheimer's disease (AD), leading to the concept of mixed dementia. Both neurodegenerative and vascular brain injuries may have an additive effect or a synergistic effect to impair cognitive functioning.[12–16] However currently no precise knowledge exists regarding the extent to which the different vascular mechanisms and types of brain changes contribute to the cognitive loss.[17]

Diagnosis

Several criteria sets for VD have been defined according to the diagnostic procedure for AD.[18–21] The main differences in the four most common sets (Table 75.2) are the definition of cerebrovascular disease (clinical and/or neuroradiological), inclusion of white matter lesions in the criteria and precision of neuroimaging findings, description of the relationship between dementia and cerebrovascular disease and temporal relation or rater judgement. Their clinicopathological validation revealed great variations in the sensitivity and specificity of diagnosing probable VD, ranging from 20 to 50% and from 84 to 94%, respectively.[22]

Because of the lack of consensus regarding both the clinical and pathological definitions, diagnosis remains problematic in clinical practice.[23] The major difficulties are to document the vascular burden in case of diffuse white matter abnormalities and to determine the implications of documented cerebrovascular and neurodegenerative lesions in cognitively impaired subjects. Neuroimaging plays a fundamental role and MRI is the ideal imaging technique for cognitive disorders. MRI provides information about brain atrophy, ventricular size, medial temporal atrophy, white matter lesions and ischaemic changes or haemorrhagic lesions, including microbleeds. The radiological procedure should include the following sequences: 3D T1-weighted, T2-weighted, fluid attenuation inversion–recovery and gradient echo.[24] To assess the likelihood of concomitant AD, clinicians can also use anamnesis (progressive onset of memory impairment), neuropsychological profile demonstrating temporal dysfunction, brain metabolism investigations with positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging and biomarkers.

Epidemiology

In epidemiological surveys, prevalence and incidence vary according to the diagnosis criteria set and the included

Table 75.2 Comparison of clinical diagnosis sets for probable vascular dementia.

Probable VD	ICD-10	DSM-IV	ADDTC	NINDS–AIREN
Dementia	Decline in memory for at least 6 months, decline in general processing of information, judgement and thinking Significant impairment of social functioning Absence of clouding of consciousness	Memory impairment ≥1 disturbances: aphasia, apraxia, agnosia, executive functioning Significant impairment of social functioning Not occurring during the course of delirium	Decline in intellectual function not isolated to a single narrow intellectual performance Broad interference with patient's customary affairs of life Independent of level of consciousness	Cognitive decline Memory impairment ≥2 disturbances: orientation, attention, language, visuospatial or executive functions, motor control, praxis Interference with activities of daily living Exclusion of delirium, psychosis, . . .
Cerebrovascular disease: clinical evidence	Evidence from history, examination or tests: Focal signs Deterioration in emotional control, social behaviour, apathy	Focal neurological signs/symptoms OR Significant cerebrovascular diseases on imaging	Evidence of ≥2 infarcts: History, neurological examination History of multiple transient ischaemic attacks, vascular risk factors Elevated Hachinski scale AND/OR Cerebrovascular lesion on CT or MRI	Clinical examination: Focal signs or gait disturbance, falls, urinary symptoms, pseudobulbar palsy, mood changes, apathy, emotional inconsistency AND Relevant cerebrovascular lesion on CT or MRI
Cerebrovascular disease: brain imaging	Helpful but not required No precision	Multiple infarcts in the cortex and subcortical white matter	≥1 infarct in the cerebellum Multiple infarcts in brain regions known to affect cognition Further research for periventricular and deep white matter changes on T2-MRI	Multiple large-vessels infarcts Single strategic infarct Multiple basal ganglia and white matter lacunes or extensive periventricular lesions
Relationship	Reasonably judged to be aetiologically related to dementia Abrupt onset, stepwise deterioration	Judged to be aetiologically related to the disturbances	Clear temporal relationship required if a single stroke	Onset 3 months after stroke Abrupt deterioration or stepwise progression

cohort (population-based, individuals with vascular risks factors, stroke cohort).[25]

In a large survey, the Cardiovascular Health Study,[25] the different criteria sets identified 9% (NINDS–AIREN), 13% (DSM-IV) and 24% (ADDTC) incident cases of probable VD. The proportion of AD was 55%, probable VD 12% and mixed dementia 33% according to the ADDTC criteria combined with the NINCDS–ADRDA criteria for AD.[26]

The prevalence of dementia 3 months after an ischaemic cerebrovascular event in a stroke cohort varied from 6% (ICD-10) to 21.1% (NINDS–AIREN) and 25.5% (DSM-III).[27] In a population-based study, the risk of dementia in the year following stroke was nine times greater than expected with a persistent increased risk after the first year.[28] Retrospective evaluation using informant questionnaires showed that one-sixth of stroke patients had previous cognitive impairment before an acute cerebrovascular event, in favour of mixed dementia.[29] Episodes of stroke are known to worsen cognitive decline in patients with pre-existing AD and the risk of AD is also significantly increased after acute events such as stroke or transient ischaemic attack.[30] Stroke subtypes, volume of damaged brain tissue, functional tissue loss and location of the lesions in strategic areas were reported to be the major determinants of dementia, with inconsistent results in neuropathological and epidemiological studies.[31] White matter changes and associated Alzheimer pathology, cardiovascular risk factors, low educational level, female gender and apolipoprotein E4 may also contribute to cognitive impairment in stroke patients.[32]

Table 75.3 Risk factors associated with vascular cognitive impairment and vascular dementia.

Hypercholesterolaemia
Hypertension
Diabetes mellitus
Metabolic syndrome
Smoking
Atrial fibrillation
Hyperhomocysteinaemia
ApoE4 polymorphism
Systemic inflammation

VD and AD share common risk factors predisposing to cerebrovascular disease and stroke (Table 75.3), their correlation with cognitive deterioration was demonstrated in longitudinal studies, offering some promise for prevention of both pathologies.[33]

Since VCI without dementia was recently identified without any agreement on diagnosis, little is known about progression and risk of VD. In a population-based study, 42% of subjects with vascular mild cognitive impairment developed dementia within 5 years.[34]

Clinical and neuropsychological features

Clinical manifestations are related to the type of cerebrovascular disease (acute or subacute) and the brain areas involved.

Some clinical symptoms, such as gait disturbances, parkinsonism, dysarthria, dysphagia, urinary incontinence and pseudobulbar palsy were previously described in Binswanger disease or lacunar state and can be observed in association with periventricular white matter lesions.[35] In the case of a progressive, slow decline of cognitive function, evidence of those signs supports the diagnosis of subcortical VD rather than AD. By contrast, hemianopsia, reflex asymmetry, hemimotor or hemisensory dysfunction and aphasia are more often observed in the case of cortical cerebral infarct.[36]

The cognitive decline observed in patients with white matter lesions has been suggested to be due to disruption of subcortical–cortical pathways producing dysfunction of frontal lobe structures. That is why the major neuropsychological feature in VCI is executive dysfunction with decreased psychomotor speed, impairment of planning and switching from one task to another, deficit in working memory and reduced verbal fluency. Since memory tasks require concomitant executive functioning, impairment in episodic memory may also be observed even without dysfunction of the medial temporal lobe. Fluctuation of performances is another key feature of VCI.

Neuropsychological testing has to be adapted to this specific profile (verbal phonemic and semantic fluencies, trailmaking test, digit symbol, etc.) as proposed by the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network.[24] For clinicians, management of patients with vascular risk factors, particularly hypertension, should include cognitive screening with the aim of detecting early signs of cognitive impairment and dementia.[37] For brief testing, the previous group suggested using the Montreal Cognitive Assessment, which is more sensitive than the Mini Mental State Examination to executive function (www.mocatest.org: free access to translations of tests and instructions for clinical and educational purposes).[38]

Finally, non-cognitive features such as apathy and depressed mood are very common in vascular cognitively impaired patients.

Preventive and curative therapies

Preventive approaches to VCI rely mainly on the identification and treatment of risk factors. Given the high proportion of dementia attributable to possibly reversible vascular causes, it has been suggested that vascular risk manipulation may result in up to a 50% reduction in the dementia prevalence rate in the elderly.[39]

Prevention strategies should focus on reduction of stroke and cerebrovascular disease, with attention to control of risk factors such as hypertension, diabetes mellitus, hypercholesterolaemia, atrial fibrillation and hyperhomocysteinaemia.

The benefit of antihypertensive drugs on dementia or cognitive decline prevention was demonstrated in three studies conducted in elderly hypertensives,[40] in high-risk subjects with previous ischaemic cerebral attack[41] and in patients with vascular disease or with diabetes associated with another vascular risk factor.[42] However, inclusion of patients with pathophysiologically heterogeneous types of vascular cognitive decline, prescription of active antihypertensive drugs in placebo groups and short duration of follow-up could explain the negative results in other studies.[43–47] Since dependency in VD is due to both cognitive impairment and stroke-related physical disability, the impact of such therapies on dependency is very positive.[48]

Studies concerning lipid-lowering agents on cognitive performance are rare. The PROSPER study did not show any effect of pravastatin on cognitive function as compared with placebo in 70–80-year-old subjects followed over 3 years.[49] Moreover, in patients with AD the LEADe study did not demonstrate any benefit regarding cognition of atorvastatin compared with placebo and anti-diabetes therapies in particular.[50]

Even though aspirin is widely prescribed in VD for stroke prevention, its effect on cognitive functioning or the impact

on prognosis remain unclear.[51,52] Considering the risk of cerebral haemorrhage in patients with amyloid angiopathy, antithrombotic agents should be used with caution when lobar microbleeds are observed on brain MRI.[53]

Whether progression of white matter lesions could be a significant surrogate endpoint with regard to cognitive protection has to be elucidated, even though promising results were observed in a study conducted with blood pressure-lowering regimen in patients with previous cerebrovascular disease.[54,55]

Early detection is important to improve the observance of the action of drugs and will become increasingly important as preventive therapies become available. In a preventive trial. the benefit of lowering blood pressure on cognitive function was even higher in hypertensive patients with previous intellectual impairment, but not in another study conducted in patients with cerebrovascular lesions and decreased levels of cognitive functioning.[56,57]

A number of drugs have also been tested with the aim of improving or slowing cognitive decline in patients affected by various forms of cerebrovascular disease. Most of these trials, using nootropics (propentofylline,[58] pentoxifylline[59]) or other metabolically active compounds (nicergoline, Ginkgo biloba[60]) or calcium antagonists (nimodipine[61]), yielded unsatisfactory results.

Since cholinergic deficits are also encountered in VD, the response to cholinesterase inhibitors was investigated, with discrepancies in the results due to heterogeneous cerebrovascular disease or mixed dementia cases in the included subjects.[62,63] Furthermore, the primary endpoint has to be adapted to the specific neuropsychometric profile of VCI. However, in a double-blind, placebo-controlled trial avoiding all these biases, donepezil did not show any significant benefit in CADASIL.[64] So far, there has been no recommendation to prescribe cholinesterase inhibitors in the pure form for VD, but they should be used in mixed dementia with both AD and VD lesions.

Similarly, insufficient benefit of memantine in mild to moderate VD was observed to be able to recommend glutaminergic therapy.[65]

Concerning other strategies, such as cognitive training or physical activity, no definite conclusion can be drawn about their efficacy on cognitive functioning in patients suffering from VD.[66] Management of depression is often difficult, with a low efficacy of antidepressants.

Conclusion

Prevention had dramatically decreased mortality due to stroke in subjects with vascular risk factors by the end of the twentieth century. However, since the beginning of the present century, VCI, a more silent and progressive disorder, has become a major public health challenge, in association with other cognitive disorders such as AD. Clinicians must pay attention to the risk of cognitive impairment in patients with vascular risk factors in order to prevent dependency due to intellectual disability. Strategies that aim to reduce this risk have to be established, with special interest in blood pressure-lowering treatments.

Key points

- VCI, with or without dementia, is defined by the loss of cognitive function resulting from ischaemic and/or haemorrhagic brain lesions due to cerebrovascular disease.
- In subjects with cardiovascular risk factors, such as hypertension, focal ischaemic lesion (lacuna) or extensive subcortical or periventricular white matter, lesions are frequent.
- Brief cognitive testing oriented to executive and episodic memory evaluation is recommended in patients with vascular risk factors to detect potentially vascular and neurodegenerative symptomatic brain lesions.
- The impact of vascular risk factor management on cognitive impairment has to be evaluated.
- The benefit of blood pressure-lowering drugs on dementia has been demonstrated in elderly hypertensive patients and in subjects with a previous cerebrovascular event.

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CHAPTER 76

Mental stimulation and dementia

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Introduction

Owing to the rapid greying of populations worldwide, dementia has become a major global public health issue. Age-associated cognitive decline and primary dementia syndromes such as Alzheimer's disease are major sources of morbidity and mortality worldwide. They pose a significant burden not only on affected individuals, but also on their caregivers and society in general. In 2006, the worldwide prevalence of Alzheimer's disease was estimated to be 26 million.[1] It has been predicted that by 2050, the prevalence of Alzheimer's disease will quadruple, by which time one in 85 persons worldwide will be living with the disease.[1] The global burden and impact of dementia coupled with the paucity of effective pharmacological interventions lends a new urgency to discover new preventive strategies for dementia. It has been estimated that if interventions could be developed to delay both disease onset and progression by a modest 1 year, there would be nearly nine million fewer cases of Alzheimer's disease worldwide in 2050.[1]

Mentally stimulating activities in this chapter are defined as those activities that individuals engage in for enjoyment, mental health and wellbeing, which are independent of work, household chores or activities of daily living. These activities are popular, enjoyable, widely available and can be easily incorporated into lifestyles. Mentally stimulating activities run the gamut from board games such as chess to card games such as bridge, reading, playing musical instruments, listening to music, knitting, painting or doing crossword puzzles. There is growing interest among the scientific community and also the general public in understanding and defining the role of mentally stimulating activities as a preventive strategy for cognitive decline.

In this chapter, types of mental stimulation interventions, supporting evidence, possible mechanisms of action, targets of intervention and steps to consider in implementing mentally simulating activities for older adults in community or clinical settings are discussed.

Cognitive (mental) interventions

Clare and Woods categorized mental stimulation interventions into three types based on the mode of delivery and the goals of the intervention: cognitive stimulation, cognitive rehabilitation and cognitive training.[2]

Cognitive stimulation refers to the involvement in group activities that are designed to increase cognitive and social functioning in a non-specific manner. Examples of cognitive stimulation activities include participation in group discussions, supervised leisure activities, list memorization with no particular support and also more structured activities such as reminiscence therapy that involves the discussion of past activities, events and experiences.

Cognitive rehabilitation involves individually tailored programmes centred on specific activities of daily life. Examples include learning the name of a new caregiver, balancing a chequebook or improving conversational fluency.[2] Cognitive rehabilitation is a more individualized approach to helping people with cognitive impairments in which those affected and their families work together with healthcare professionals to identify personally relevant goals and devise strategies for addressing these. The emphasis of cognitive rehabilitation is not on enhancing performance in cognitive tasks as such, but on improving mental functioning of the patient in realistic situations.

Cognitive training involves teaching theoretically motivated strategies and skills in order to optimize cognition functioning. Cognitive training is most often provided individually or in small groups. Cognitive training typically involves guided practice on a set of standard tasks designed to reflect particular cognitive functions, such as memory, attention or problem solving. The underlying assumption is that practice has the potential to improve or at least maintain functioning in the given cognitive domain. The training is occasionally facilitated by family members with therapist support. Tasks may be presented in paper-and-pencil or computerized form or may involve analogues of activities

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of daily living. Usually a range of difficulty levels is available within a standardized set of tasks to allow for selection of the level of difficulty that is most appropriate for a given individual. The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Study, which randomized 2832 non-demented elderly participants to a 6 week intervention, focused on memory, reasoning and speed of processing, is an example of this form of intervention.[3]

Supporting evidence

Support for the potential role of mentally stimulating activities in preventing or mitigating cognitive decline comes from animal studies and also observational studies in humans and, to a lesser extent, randomized clinical trials.

Animal studies

Exposure to environments enriched with various sensory stimuli and motor demands (*enriched environment*) is considered the animal equivalent of participation in mentally stimulating leisure activities by humans, although obvious species differences limit direct extrapolation of findings from rodents to humans.[4] In the 1960s, Rosenzweig and colleagues reported changes in brain neuroanatomy and neurochemistry in rats exposed to enriched environments, including increased cerebral cortex thickness.[5,6] In the 1970s, Greenough *et al*. reported finding greater synapse density, glial cell proliferation and structural changes in nerve cells, including increased dendritic branching in rats exposed to enriched environments compared with rats living in standard housing.[7] Recent studies have found increases in levels of acetylcholine, a neurotransmitter involved in cognition and in various neurotrophic factors, in rodents exposed to enriched environments.[4] Environmentally enriched conditions have been shown to reduce cognitive deficits in young and adult animals.[4] Neurogenesis has been demonstrated not only in the adult rodent hippocampus, olfactory bulb and cerebral cortex, but also in primates and humans.[4,8] These findings indicate a substantially important role of the external environment in inducing neurochemical, morphological and behavioural changes in the brain.[4,8]

Observational studies

There is increasing evidence for the role of lifestyle factors as moderators of differences in cognitive ageing and as protective agents for the development of Alzheimer's disease from observational studies in older adults. Lifestyle factors that have been extensively studied in the context of cognitive decline include education, occupational status and participation in leisure activities. Previous observational studies have found that high levels of participation in mentally stimulating leisure activities decreased the risk of dementia or cognitive decline. For instance, one study found leisure activities such as travelling, doing odd jobs, knitting and gardening to be associated with a reduced risk for dementia. In another study, frequency of participation in common cognitive leisure activities (e.g., reading books; playing games such as cards, checkers/draughts, crosswords or other puzzles; and going to museums) was assessed at baseline for 801 elderly Catholic nuns, priests and brothers without dementia.[9] During follow-up, a one-point increase in the cognitive activity score was associated with a 33% reduction in the risk for Alzheimer's disease. Additionally, engagement in cognitive leisure activities was also associated with slower rates of cognitive decline. In another prospective study, participation in a variety of leisure activities characterized as either intellectual (such as reading, playing games or going to classes) or social (such as visiting friends or relatives, going to movies or restaurants or doing community volunteer work) was assessed in a population study of 1772 non-demented elderly people living in New York city.[10] During follow-up, subjects who reported higher levels of participation in these activities at baseline had a 38% less risk of developing dementia.

Table 76.1 summarizes our own experience in assessing the association between participation in mentally stimulating activities and risk for various cognitive syndromes in a cohort of older adults participating in the Bronx Aging Study. The Bronx Aging study enrolled community residing subjects between 75 and 85 years of age.[11] Exclusion criteria included severe visual or hearing loss, idiopathic Parkinson's disease, liver disease, alcoholism or known terminal illness. Subjects were screened to rule out the presence of dementia. The inception cohort was middle-class, predominantly Caucasian (91%) and mostly women (64%). Self-reported frequency of participation in leisure activities was coded to generate a scale with one point corresponding to participation in one activity for one day per week.[12] For each activity, subjects received seven points for daily participation, four points for participating several days per week, one point for weekly participation, and zero points for participating occasionally or never. The number of activity days for each activity was summed to generate a Cognitive Activity Scale. Participants received detailed clinical, medical and cognitive assessments at baseline and at 18 -month follow-up visits. Over the study follow-up, a one-point increase in Cognitive Activity Scale scores was associated with reduced risk of developing not only various dementia syndromes[12] but also intermediate cognitive impairment states such as mild cognitive impairment (MCI) syndrome,[13,14] as presented in Table 76.1.

Table 76.1 Participation in mentally stimulating activities and risk of cognitive syndromes in the Bronx Aging Study[a].

Syndrome	Hazard ratio	95% CI
Any dementia[12]	0.93	0.89–0.96
Alzheimer's disease[12]	0.93	0.88–0.98
Vascular dementia[12]	0.92	0.86–0.99
Amnestic mild cognitive impairment syndrome[13]	0.95	0.91–0.99
Vascular cognitive impairment syndrome[14]	0.93	0.89–0.97

[a]Hazard ratios and 95% confidence intervals (CI) are reported for each one-point increase in the Cognitive Activity Scale score and were obtained from Cox proportional hazard models adjusted for several potential confounders such as age, gender, education and the presence or absence of medical illnesses.

Clinical trials

Numerous cognitive training interventions have been conducted in laboratory or small-scale clinical settings. In general, these studies showed that cognitive training helps normal elderly individuals to improve performance on the specific task for which they were trained as compared with untrained individuals. Near transfer of training effects refers to improvements in cognitive domains that are closely related to the cognitive processes trained. Far transfer refers to improvements in domains that are distal from the cognitive processes trained. Although some studies showed that near transfer effects can be retained for months,[15] no-one has conclusively proved that the improvement in any of the cognitive domains can be transferred to real-world situations.

The ACTIVE study reported beneficial effects on cognition in 2832 non-demented older adults following a 6 week cognitive training intervention, especially in the cognitive domains directly related to the intervention, and these effects were found to last up to 5 years. There were also modest effects on everyday functioning.[3,15] A randomized controlled study in 487 older adults that compared an 8 week computerized cognitive training programme with a general cognitive stimulation programme found that the intervention group improved on untrained measures of memory and attention.[16] In contrast, a 6 week study in which 11 430 participants self-trained three times each week for a minimum of 10 min per day on online cognitive tasks showed improvements in tasks trained, but no evidence was found for transfer effects to untrained tasks.[17] This study included participants with a wide age range (18–60 years), training sessions were not supervised and the duration of training (dose) was not standardized across participants, which may limit the generalizability of the results of this study to elderly populations.

The above clinical trials enrolled elderly individuals without dementia. Another clinical trial reported the effect of a programme of mental stimulation in nursing home residents with Alzheimer's disease. Following the intervention, the 115 Alzheimer's disease patients who received mental stimulation therapy showed improvements in global measures of cognition and also in quality of life compared with the 86 Alzheimer's disease patients in the usual care control group.[18] This trial indicates that engagement in mentally stimulating activities may have behavioural benefits beyond cognition.

Mechanisms

Given the wide range of mentally stimulating activities available to older adults, it is likely that multiple mechanisms are involved in the cognitive benefits reported in previous observational studies. The three main mechanisms that have often been invoked to explain cognitive benefits of mentally stimulating activities are improving or building cognitive reserve, improving vascular health or mitigating effects of vascular insults to the brain and via stress mechanisms.

Cognitive reserve

The concept of cognitive reserve has been proposed to account for the fact that there is no direct relationship between the degree of brain damage or pathology and its clinical manifestations. For example, a head injury of the same magnitude can result in different levels of cognitive impairment in different individuals. Several prospective studies of ageing have reported that up to 25% of older adults whose neuropsychological testing is unimpaired prior to death meet full pathological criteria for Alzheimer's disease,[19] suggesting that this degree of pathology does not invariably result in clinical dementia.

Cognitive reserve postulates that individual differences in the cognitive processes or neural networks underlying task performance allow some people to cope better than others with brain damage. Katzman proposed that highly educated individuals are more resistant to the effects of dementia as a result of having greater cognitive reserve and increased complexity of neuronal synapses.[20] When regional cerebral blood flow was compared in different groups of Alzheimer's disease patients with the same degree of cognitive deterioration but different levels of education, it was observed that the patients with a high level of education had a more severe deficit of parietotemporal perfusion, indicating that Alzheimer pathology was more advanced in these subjects.[21]

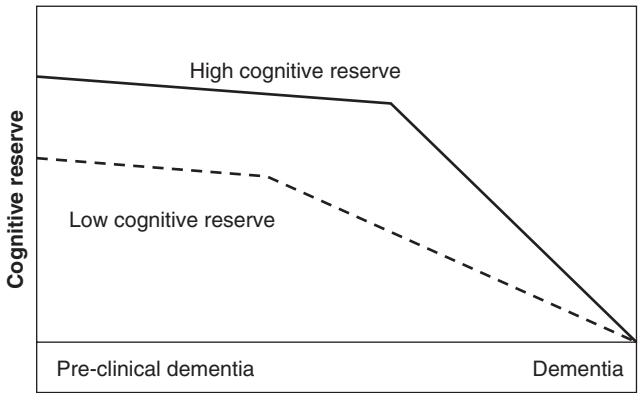

Figure 76.1 Cognitive reserve.

Figure 76.1 illustrates a hypothetical scenario comparing two older adults with high and low levels of cognitive reserve. The individual with higher cognitive reserve, who is able to resist the effects of dementia longer, develops cognitive decline later in life compared with the individual with low cognitive reserve. Since the duration of the dementia is assumed to be similar in both individuals, the patient with higher cognitive reserve will decline more rapidly than the patient with low cognitive reserve once that subject starts to manifest clinical symptoms.

Stern hypothesized that the neural implementation of cognitive reserve takes two forms, neural reserve and neural compensation.[22] In *neural reserve*, pre-existing brain networks that are more efficient or have greater capacity are less susceptible to disruption by age-related pathology such as Alzheimer's disease. Although healthy individuals may utilize these networks when coping with increased task demands, the networks could also help an individual cope with increasing brain pathology. In *neural compensation*, alternative brain networks compensate for pathology's disruption of pre-existing brain networks. Older adults show less specificity in many cognitive operations than young adults in brain regions that are recruited to carry out that task. This dedifferentiation has also been interpreted by some researchers as a compensatory function.

Accumulating evidence concerning brain plasticity in adults demonstrates the existence of several mechanisms that may augment cognitive reserve: angiogenesis, synaptogenesis and neurogenesis.[8] The widely held belief that the adult brain cannot develop new neurons is challenged by an increasing number of observations that at least some regions of the adult brain can respond to environmental stimuli by adding new neurons.[8]

Vascular

In the Bronx Aging Study, older adults who reported high levels of participation in cognitive leisure activities were at reduced risk of developing vascular cognitive impairment syndrome (cognitive impairment that is caused by or associated with vascular risk factors) with and without dementia.[14,23] Epidemiological studies have suggested that vascular disorders and vascular risk factors are involved in the pathogenesis and progression of Alzheimer's disease. Evidence from experimental, neuropathological and epidemiological studies supports both a direct or indirect effect of severe atherosclerosis on dementia and Alzheimer's disease in older adults.[23,24] As there is substantial clinical and neuropathological overlap between Alzheimer's disease and other dementias, the additive or synergistic interactions between vascular factors and Alzheimer pathology may be relevant in the clinical expression of dementia syndromes including Alzheimer's disease.[24,25] Mentally stimulating activities might be markers for healthy ageing; older adults who take part in mentally stimulating activities might also exercise more, have healthy diets or manage their comorbid medical illness better. Mentally stimulating activities may also promote vascular health by improving cognitive functions that are necessary to manage activities of daily living successfully. Interestingly, exposure to enriched environments was reported to improve functional outcomes after experimental brain infarctions in animal models.[4,26] This result suggests that mentally stimulating activities may help mitigate the effects of vascular insults to the brain, although this association has not been established in humans.

Stress

A high proneness to stress has been reported to be associated with increased risk of developing Alzheimer's disease.[27] The hippocampus is involved in stress response via glucocorticoids. Corticosterone hypersecretion due to stress downregulates hippocampal steroid receptors, which in turn can damp the feedback inhibition of the adrenocortical axis, leading to further hypersecretion, which finally can cause permanent loss of hippocampal neurons.[28] Associations between elevated cortisol levels, impaired cognitive function and hippocampal atrophy have been found in human studies involving dementia, depression, post-traumatic stress disorder and Cushing's disease.[28] Individuals who actively engage in mentally stimulating activities have more frequent contacts and have more opportunities to engage with others, leading to positive emotional states such as self-esteem, social competence and adequate mood, which lead to lower stress.

Targets of intervention

Disease prevention involves governments, professional organizations, public health professionals, healthcare

Table 76.2 Levels of prevention.

Level of prevention	Target population	Goals
Primary	Healthy seniors 'Worried well'	Prevent development of dementia Prevent age-associated cognitive decline
Secondary	Mild cognitive impairment (MCI) syndrome	Prevent conversion to dementia Prevent further cognitive decline
Tertiary	Dementia Alzheimer's disease	Prevent further cognitive decline Prevent behavioural disturbances Improve quality of life

professionals and individuals working at three levels to maintain and improve the health of individuals and communities. The first level, known as primary prevention, aims to prevent the development of disease before it occurs by eliminating or treating specific risk factors which may decrease or delay the development of disease, and usually targets healthy individuals. Secondary prevention refers to measures that target interventions at the preclinical stages of the disease, which is identified by clinical markers or biological tests. Tertiary prevention efforts focus on people already affected by disease and attempts to reduce resultant disability and restore functionality.

Table 76.2 lists target audiences and goals for each of these levels of prevention in the context of cognitive decline and dementia in older adults. Most drugs currently available for treating dementia patients have modest effects at best and do not substantially impact disease progression. Hence all forms of prevention for cognitive decline and dementia need to be explored more rigorously.

Implementing interventions

Exercise interventions are typically described in terms of dose ('how much?'), frequency ('how often?') and intensity ('how hard?'). There is limited evidence to recommend optimal dose, frequency and intensity for mentally stimulating activities to prevent cognitive decline. Although the optimal dose (how much?) of mental stimulation has not been established, findings from recent studies suggest that short duration of training or infrequent number of sessions may not be adequate to provide meaningful cognitive benefits.[2,16,17] In the Bronx Aging Study, participants whose cognitive activity levels were in the top third (greater than 11 points) of the group had a 63% reduced risk of dementia compared with those with activity levels in lowest third (fewer than 8 points).[12] Even participants with activity levels in the middle third (8–11 points) had a 52% reduced risk of dementia compared with those in the lowest third. These results indicate that the higher the frequency of participation, the better are the cognitive benefits of mentally stimulating activities.

Although engagement in mentally stimulating activities carries a very low risk of side effects, it is possible that some patients, who have not previously engaged in these types of activities, may be intimidated or stressed by starting these activities for the first time. Hence it is important to tailor mentally stimulating activities to the skill level and interests of the individual. The goal is to maximize participation and also the degree of mental stimulation. Depending on available resources or opportunities, patients could participate in these activities at home, local senior centres or in nursing home settings. The activities could be done either alone or with supervision. Formal cognitive rehabilitation programmes supervised by health professionals are also another option.

A discussion with the individual and/or family will be helpful in discovering current hobbies and interests or possible new areas or activities that might be of interest to the individual. It is important for the individual to choose mentally stimulating activities that are not only enjoyable, but also challenging. If a particular activity does not suit a patient, then they could be encouraged to try another mentally stimulating activity. Gradually increasing the duration and the level of difficulty of the activity will help prevent dropout. Involving the family and caregivers in the process is also important to ensure that the patient maintains participation. In the Bronx Aging Study, reading, playing board games such as chess or card games such as bridge and playing a musical instrument were the individual mentally stimulating activities that were associated with reduced risk of dementia.[12] However, other mentally stimulating leisure activities such as gardening, travelling, visiting museums or doing crossword puzzles have also been found to have beneficial effects on cognition in other epidemiological studies. Leisure activities that combine physical and mental effort, such as dancing, have also been reported to have cognitive benefits.[12] The use of computerized 'brain fitness' programmes have also become more popular in recent years.[16] A United States Census Bureau community survey in 2003 reported that 35% of adults over age 65 years and 63% of adults between ages 55 and 64 years had a computer at home, indicating a huge potential audience for computerized brain fitness programmes. It has been our experience that basic computing skills to play computerized brain games can be taught to older adults who are computer novices in one or two sessions. Hence the choice of mentally simulating activity may

be less important than the dose, frequency and intensity of participation.

Conclusion

There is a paucity of high-quality clinical trials of mental stimulation in dementia. Large-scale population-based studies and controlled clinical trials are critically needed to investigate strategies to maintain cognitive function in individuals at risk for decline, to identify factors that may delay the onset of Alzheimer's disease among individuals at risk and to identify factors that may slow the progression of Alzheimer's disease among individuals already diagnosed with the disease.

Key points

- Observational studies support a link between increasing levels of participation in mentally stimulating activities and reduced risk of cognitive decline and dementia.
- Mentally stimulating activities may exert their protective effects on cognitive decline via improving cognitive reserve, promoting vascular health and reducing stress.
- Given the low risks associated with participation in mentally stimulating activities, clinicians should consider encouraging participation of older adults in such activities. The specific activities recommended should be tailored to the individual's interests, capacities and background. The duration and degree of difficulty of the activity should be gradually increased to provide increasing levels of challenge.
- However, it should be noted that there is a paucity of high-quality clinical trials of mental stimulation in dementia to support evidence-based recommendations at present.

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CHAPTER 77

Exercise and dementia

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Introduction

The incidence and prevalence of dementia are expected to increase dramatically in the coming decades. In the absence of curative treatment, risk factor modification remains the cornerstone for dementia prevention. Population studies and randomized controlled trials have recently indicated that people who are cognitively, socially and physically active have a reduced risk of cognitive impairment. Dementia is now considered as a long process resulting from accumulation of both risk and protective factors during lifespan (Figure 77.1).[1] Physical activity appears to be one of the main factors that contribute to the maintenance of a healthy ageing brain. Basic research trials also confirmed that an enriched environment and physical activity enhance the proliferation of new brain cells and promote brain repair in animal models.[2] Some of the most promising strategies for the prevention of dementia include vascular risk factor control, but also cognitive activity and physical activity.

Physical activity is already known as a cost-effective practice that has demonstrated during the past 30 years numerous physical benefits in the field of heart disease and cancer. The benefits of physical activity on brain functioning have been reported more recently.

Results from clinical and basic research facilitated by new technological approaches such as functional magnetic resonance imaging (fMRI) support the benefit of physical activity on cognitive decline in humans. However, none of the clinical research has clearly demonstrated that physical activity can prevent dementia. Nevertheless, growing evidence supports the view that physical activity may, at least, slow cognitive decline. Even a small delay of the onset of cognitive decline or a slowing of the disease progression would have a significant impact on this major public health priority.

Physical activity has also been shown to improve function even in frail nursing home residents[3] and Alzheimer's disease (AD) patients.[4] Physical activity yields an important and potent protective factor against functional decline and various frequent and devastating complications of the disease such as falls, fractures, malnutrition and behavioural disturbances, such as depression and anxiety. For demented patients, physical activity may also prevent key problems and have a major impact on the burden of the disease and quality of life.

Physical activity and the prevention of dementia in clinical research

Evidence that physical activity prevents cognitive decline is difficult to obtain. Results from epidemiological studies must be considered carefully as numerous biases may influence the relationship between exercise and the risk of dementia: the lifestyle of sedentary participants usually differs from that of exercisers in many ways. Many potential confounders between physical activity and the risk of dementia exist. Moreover, in most epidemiological studies, the assessment of physical activity is questionable. Involvement in physical activity varies substantially during a lifetime. The assessment of physical activity may not correspond to the mean long-term regular activity and even less to activity over the subject's past lifetime. Conclusions about the impact of different types, intensity and duration of the past physical activity are even more difficult to draw. An important limitation of most epidemiological studies is also that elderly subjects in the preclinical stage of dementia usually reduce their physical activity. Inactivity is a symptom frequently reported in the early phase of dementia rather than a risk factor. Behaviour disturbances such as depression or apathy usually precede the diagnosis of dementia and result in low physical activity. Finally, it is nearly impossible to discriminate between the effects of physical activity *per se* and the effects related to cognitive stimulation during physical activities that involve cognitive functions. It is therefore difficult to ascertain the specific effects of mobility and energy expenditure on brain functioning.

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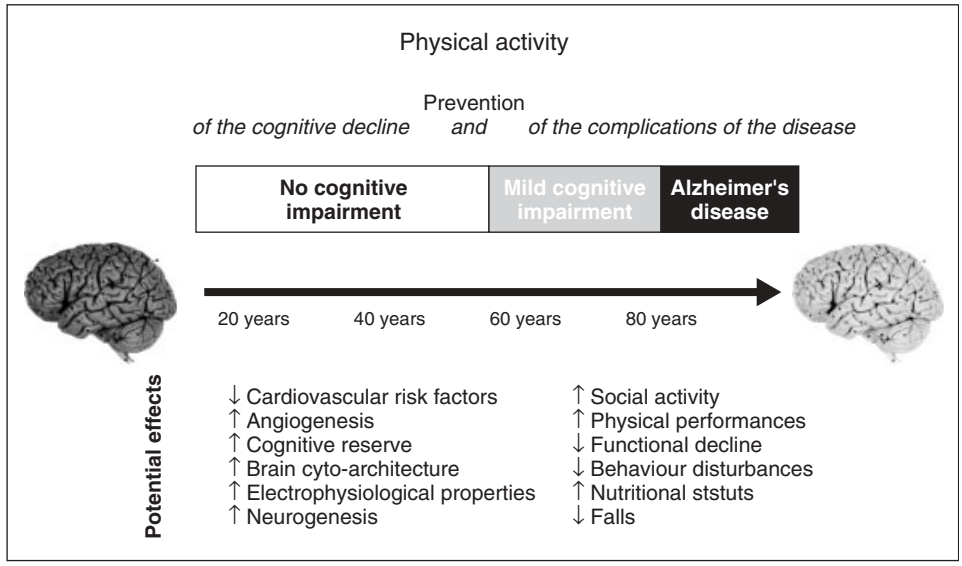

Figure 77.1 Alzheimer's disease and the potential roles of physical activity during lifespan.

Despite these limitations, many authors have examined the association between participation in physical activity and cognitive function in large groups of elderly people. Most of the time, the relationship between participation in physical activity and cognitive function is strong. Physically active aged individuals performed better in cognitive tests than their sedentary counterparts, especially in executive tests.[5] In several cross-sectional studies, cardiovascular fitness was associated with attention and executive function or visuospatial function. However, the cross-sectional design of these studies precludes inferences about causality in the relationship between physical activity and cognitive function. These cross-sectional studies are also subject to important methodological bias.

Table 77.1 reports most of the longitudinal epidemiological studies published during the past 10 years which have evaluated the association between physical activity and dementia or cognitive decline. Most of these epidemiological studies were controlled for potential confounders and suggest a protective effect of physical activity.

Currently, no randomized controlled trial (RCT) has ever concluded that physical activity prevents dementia or AD. Several randomized trials have reported a beneficial effect of a physical exercise programme on the cognitive performances of non-demented participants whereas other randomized trials have reported no cognitive improvement after a physical activity programme. None of these trials were designed to assess incidence of AD or dementia as the main outcome.

In 2003, Colcombe *et al*.,[24] in a meta-analysis of 18 interventional studies with a randomized design published between 1996 and 2001, Christie concluded that there is a significant effect of aerobic exercise training on cognitive function. In a Cochrane review published in 2008, Angevaren *et al*.[25] assessed the effectiveness of physical activity on cognitive function in people older than 55 years of age without known cognitive impairment. Eight out of 11 RCTs that compared aerobic physical activity programmes with any other intervention or no intervention reported an improvement in cognitive capacity that coincided with the increased cardiorespiratory fitness of the intervention group.

Since the above meta-analysis and systematic review, three large RCTs have reinforced these conclusions in non-demented elderly persons but also in patients with mild cognitive impairment (MCI). Patients with MCI are known to be at high risk for cognitive decline and AD and may be a target population for prevention programme.

Lautenschlager *et al*. reported that about 20 min per day of physical activity improved the cognitive function of 170 older adults with MCI.[26] The size of the effect of 6 and 18 months of a physical programme was modest but comparable to the benefit usually reported with the use of donepezil. Other authors have also reported that a high-intensity aerobic exercise programme (75–85% of heart rate reserve for 45–60 min per day, 4 days per week for 6 months) results in an improvement of executive control processes in older women with MCI.[27]

Finally, in the Lifestyle Interventions and Independence for Elders pilot (LIFE-P) study, 102 older adults at risk for mobility disability were randomized to a moderate-intensity physical activity intervention during 1 year. It was reported that the improvements in cognitive scores were associated with improvements in physical function.[28]

Table 77.1 Observational epidemiological studies on physical activity and risk of dementia or cognitive decline.

Study	Longitudinal non-demented population-based study	Summary of major findings (adjusted for confounders)
Physical activity as a significant preventive factor for dementia		
Hisayama Study (Yoshitake, 1995)[6]	828 individuals aged 65 years or over	Physical activity was associated with reduced risks of AD
Paquid study (Fabrigoule, 1995)[7]	2040 individuals aged 65 years or over	Physical activity was associated with reduced risks of dementia
Canadian Study of Health and Aging (Laurin, 2001)[8]	6434 individuals aged 65 years or over	High levels of physical activity were associated with reduced risks of cognitive impairment, AD and dementia of any type
Health Care Financing Administration Study (Scarmeas, 2001)[9]	1772 individuals aged 65 years or over	Leisure physical activities (walking for pleasure or going for an excursion) were associated with reduced risks of dementia
Bronx Aging Study (Yamada, 2003)[10]	469 individuals aged 75 years or over	Dancing was the only physical activity associated with a lower risk of dementia
Honolulu–Asia Aging Study (Abbott, 2004)[11]	2257 men aged 71–93 years	Walking more than 2 miles per day was associated with a lower risk of dementia
Cardiovascular Health Cognitive Study (Podewils, 2005)[12]	3375 individuals aged 65 years or over	Individuals engaged in more than four physical activities had lower risk of dementia
Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE) (Rovio, 2005)[13]	1449 individuals aged 65–79 years	Leisure-time physical activity, at least twice per week, was associated with a reduced risk of dementia and AD
The INVADE Study (Etgen, 2010)[14]	3903 individuals aged 55 years or over	Moderate or high physical activity was associated with a reduced incidence of cognitive impairment
Adult Change in Thought (Larson, 2006)[15]	1740 individuals aged 65 years or over	Physical activity at least three times per week was associated with a reduced risk of dementia
Physical activity as a non-significant preventive factor for dementia		
Sydney Older Persons Study (Broe, 1998)[16]	327 individuals aged 75 years or over	No statistically significant association between physical activity and dementia
Radiation Effect Research Foundation Adult Health Study (Yamada, 2003)[10]	1774 individuals	No statistically significant association between physical activity and dementia
Kungsholmen Project (Wang, 2002)[17]	776 individuals aged 75 years or over	Daily physical activity was associated with a no significant reduction risk of dementia
Physical activity as a significant preventive factor for cognitive decline		
MacArthur Study (Albert, 1995)[18]	1192 individuals aged 70 to 79 years	Strenuous physical activity was associated with a reduced risk of cognitive decline
Study of Osteoporotic Fractures (Yaffe, 2001)[19]	5925 individuals aged 65 years or over	Highest quartile of blocks walked per day was associated with a lower risk of cognitive decline
Brescia Study (Pignatti, 2002)[20]	364 individuals aged 70–85 years	Inactivity was associated with a higher risk of cognitive decline
Sonoma Study (Barnes, 2003)[21]	349 individuals aged 55 years or over	High peak oxygen consumption (VO_2) was associated with a lower risk of cognitive decline
Monongahela Valley Independent Elders Survey (MoVIES) (Lytle, 2004)[22]	1146 individuals aged 65 years or over	Exercising five times per week or more was associated with a lower risk of cognitive decline
Nurses' Health Study (Weuve, 2004)[23]	18 766 women aged 70–81 years	Walking at least 1.5 h per week at a pace of 21–30 min per mile was associated with a lower risk of cognitive decline
Physical activity as non-significant preventive factor for cognitive decline		
Sydney Older Persons Study (Broe, 1998)[16]	327 individuals aged 75 years or over	No statistically significant association between physical activity and cognitive decline

Physical activity and executive function

Most of the epidemiological studies and RCTs support the idea that the effects of physical activity were greatest for those tasks involving executive control processes.[24] Physical activity may influence structures and functions of the brain differently than other stimulation such as cognitive stimulation. In the MOBILIZE Boston Study, the neuropsychological executive tests were positively associated with participation in physical activity. In contrast, delayed recall of episodic memory was not associated with physical activity.[5] Other studies have reported that aerobic exercise intervention enhances executive function, whereas other cognitive functions seem to be less sensitive or insensitive to physical exercise. Using fMRI, it was recently demonstrated that physical activity enhances plasticity in prefrontal cortical regions that support executive function.[29] A physical activity programme also results in an increased grey matter volume mainly in prefrontal and cingulate regions and changes in brain-derived neurotrophic factor (BDNF) levels.[30] Colcombe *et al*.[24] reported that fitter older subjects had a greater grey matter volume in the prefrontal, parietal and temporal regions and a greater white matter volume in the genu of the corpus callosum than their less fit counterparts after controlling for potential confounders. These regions of the brain may retain more plasticity. These results support the notion of a specific biologically determined relationship between executive function and physical activity.

Further research is still required to increase our knowledge regarding the relationship between exercise and cognitive function in humans. However, clinical research and recent research on neuroimaging provide convincing support for the hypothesis that physical activity affects cognitive and neural plasticity in later life and prevents age-related cognitive decline.

Frailty, physical activity and cognitive reserve

Frailty is a clinical syndrome manifested by weight loss, weakness, fatigue, slow walking speed and low physical activity. These factors diminish the physiological reserves in elderly patients and put them at risk for adverse health outcomes such as disability, hospitalization and death when confronted by a stressor. Frailty has also been reported to be an independent predictor of cognitive decline[31] and dementia.[32] Low physical activity is one of the main factors for poor physical performances and frailty. Observation studies have reported that high physical performances are associated with lower rates of cognitive decline and dementia. A poor score on tests such as walking speed or poor results on the timed chair–stand test, standing balance or grip strength tests or other strength tests is associated with higher rates of cognitive decline and dementia. No study has reported that the prevention of frailty results in a reduced risk of dementia or cognitive decline. However, these studies support the hypothesis of a cross-talk between muscles and the central nervous system and that high functioning improves the cognitive reserve.

A higher cognitive reserve may help the subject engaged in regular physical activity to cope with the first cognitive symptoms of AD. This effect may delay the onset of the clinical manifestations of the disease, which may become apparent only later. Recent basic research has yielded convincing arguments that physical activity acts as a stimulus of neurogenesis, enhances the brain cytoarchitecture and electrophysiological properties and may influence neuropathological processes such as the formation of β-amyloid protein during AD.

Biological mechanisms of physical activity in preventing cognitive decline

Numerous hypotheses have been put forward to explain the relation between physical activity and brain function. Physical activity could protect against cognitive decline and dementia through a reduction of various cardiovascular risk factors such as hypertension, diabetes, hypercholesterolaemia and obesity. However, most epidemiological studies report a protective effect after adjustment for these cardiovascular risk factors, suggesting that physical activity has an independent preventive role. A review published in 2007 by Cotman *et al*.[33] examined the multiple underlying mechanisms promoted by physical activity to ensure brain health. Growing evidence from animal research suggests that physical activity directly modulates in the central nervous system, angiogenesis, neurogenesis and synaptogenesis. These responses to stress stimulated by physical activity may explain brain plasticity. Participation in physical activity may thus lower the risk of cognitive decline and dementia by improving cognitive reserve.

During a motor task and also for a brief period after a physical activity session, a transient increase in cerebral blood flow is observed in humans. In rats, aerobic training also enhances vascularization of the motor cortex but also of other regions of the brain. Angiogenesis may occur when the levels of neuronal activity of an area of the brain require an increased amount of oxygen that cannot be sufficiently delivered by the vessels. The lack of sufficient vascularization leads to the formation of new blood vessels and this occurs even in the elderly. During this process, the vascular endothelial growth factor (VEGF) seems to play an important role.[34]

In 1999, van Praag *et al*. reported that an exercise wheel enhances neurogenesis in mice.[2] Subsequent studies have confirmed that physical activity acts on proliferating precursor cells inducing neurogenesis.[34] Growing evidence

suggests that this neurogenesis process integrates the neural networks which become functional. The neurogenesis seems to be mediated by many substances such as insulin-like growth factor 1 (IGF-1) and the brain-derived neurotrophic factor (BDNF). The neurotrophin BDNF is considered to be a crucial factor upregulated by physical activity.

The role of physical activity in synaptogenesis seems to be less important. Several studies have suggested that physical activity prevalently acts on neurogenesis whereas cognitive stimulation promotes synaptogenesis.[34]

Clinical practical applications: physical activity and prevention of AD

The basic recommendations from the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) are to do moderately intense cardio training 30 min per day, 5 days per week *or* do vigorously intense cardio training 20 min per day, 3 days per week *and* do 8–10 strength training exercises per week, with 8–10 repetitions of each exercise. However, it remains actually unclear how much, what type and at what time of lifespan physical activity is optimally effective in preventing cognitive decline and dementia. No specific guidelines with a view to preventing cognitive decline, dementia or AD have been released.

Exercise programmes and assessment vary widely across experiments. Hence current epidemiological, interventional and animal studies can only suggest conditions under which physical activity (intensity, type, frequency and duration) may reduce the risk of dementia. The optimal exercise programme that would produce the maximal benefits is not known. This information may have important implications for the prevention of cognitive decline in the elderly. It also remains to be determined whether voluntary and forced exercise results in the same improvement.

Intensity and frequency

A relevant measure of intensity and duration or a standardized physical activity assessment scale is generally lacking in most longitudinal studies. They have not been designed to determine a threshold of physical activity that starts to protect against cognitive decline or AD.

Whether low-intensity physical activity, such as walking, cycling or swimming, or high-intensity activity, such as weight training, protects brain function is an important practical question. Some authors have reported that strenuous, but not moderate, physical activity was associated with less cognitive decline in a prospective study. However, organizing high-intensity activity may be challenging in frail elderly. Recommendations on physical activity have to be easily adopted by the population to be relevant.

Most epidemiological data suggest that the intensity threshold of physical activity required for a statistically significant impact on cognitive decline or dementia prevention is low. Physical activity such as playing golf, walking 1.6 km per day, playing tennis twice per week, walking at least 1.5 h per week at a pace of 21–30 min per mile, doing at least 15 min of activity at a time, three times per week, and per year amongst the physical activities walking, hiking, cycling, aerobics or calisthenics, swimming, water aerobics, weight training or stretching or other exercise was associated with a significantly lower risk of dementia in several epidemiological studies. In the LIFE pilot study, persistent engagement in physical activity was associated with beneficial effects on psychomotor processing speed and brain activation, even for moderate levels.[35]

Colcombe *et al*. also reported that a 1 h aerobic exercise training session [40–50% heart rate (HR) reserve increasing to 60–70% HR reserve over the course of the trial] three times per week over 6 months increased brain volume.[36] In this study, no dose-related response between physical activity and prevention of cognitive decline was found.

In the INVALIDE study, moderate activity (physical activity such as <3 times per week) and high activity (physical activity ≥ 3 times per week) was associated with a reduced incidence of cognitive impairment after 2 years in a large population-based cohort of elderly subjects.[14] Once again, no dose–response relationship between physical activity and incident cognitive impairment was found. In a recent interventional study, it was reported that physical activity conveys beneficial effects on memory function independently of its intensity, possibly mediated by local grey matter volume and neurotrophic factors.[30]

Other authors have reported significant trends for increased protection with greater intensity of physical activity. In the Canadian Study of Health and Aging, regular physical activity was associated with a lower risk of AD than no activity. In addition, an increased level of physical activity was associated with a decreased risk of cognitive impairment and dementia. In this cohort, risk of AD was reduced by half in subjects with higher levels of physical activity.

These results all suggest that the threshold of intensity that reduces the risk of cognitive decline and dementia is probably low. Previous studies have suggested that moderate activity could reduce dramatically the risk for other chronic diseases such as coronary heart disease. The same seems to be true for brain health. It should also be stated that, besides the benefit on brain health, exercise does not have to be performed at a specific intensity to confer a significant health benefit. However, the optimal intensity of physical activity required to maximize the slowing of cognitive decline and reduce the risk of dementia remains unclear.

Type of activity

The ACSM and the Centers for Disease Control (CDC) suggest that the benefit of physical activity is related to the amount of activity per day (energy expenditure), rather than to the type and modality of activity. Most epidemiological studies have investigated the role of physical activity on cognition using a composite score. None of these approaches make it possible to assess the influence of any specific activity on cognition.

Some specific physical activities may result in better brain functioning through social interaction and cognitive training. The psychological dimension of physical activity appears to be an important issue. In rodents, voluntary exercises have more benefit than forced exercises. Engagement in various physical activities, but not total energy expenditure, was significantly associated with the risk of dementia in the Cardiovascular Health Cognition Study (CHCS). Compared with participants engaged in one or no activity, the risk of dementia decreases by half in those engaged in four or more different activities, even after adjustment for energy expenditure. In the Bronx Aging study, dancing was the only physical activity that significantly reduced the risk of dementia.

Amongst the 13 different leisure activities of the Health Care Financing Administration (HCFA) study, walking for pleasure or going for an excursion was one of the activities the most strongly associated with a reduced risk of incident dementia. These results reinforce the hypothesis that physical activity may impact on cognition through its social interactions or cognitive training during the activity. However, other studies also suggest that simple tasks of a physical activity programme such as walking prevent cognitive decline.

Duration

Most of the studies that have investigated the association between mid-life physical activity and cognitive impairment have found that mid-life activity is associated with a lower incidence of both AD and all-cause dementia. A meta-analysis concluded that people who were not previously physically active can show improved cognitive functioning after exercising for as little as 4 months.[25]

Currently, we do not know at what period of life physical activity may have the most benefit against the risk for dementia. However, the pathophysiological process of AD begins long before cognitive decline is evident and the diagnosis established. It is probably necessary to begin being physically active early in life. According to the cognitive reserve hypothesis, physical activity performed across the whole lifespan may contribute to maintaining cognitive function in old age.

Physical activity in AD populations

Several studies have also confirmed the benefit of physical activity in older adults with dementia.[25,37] Older people with poor cognition had a steeper decline in physical performance than those with good cognition. Falls, malnutrition, behavioural disturbances or depression are frequent and severe consequences of the disease. These complications of the disease result in a high rate of functional decline. Their prevention may improve the course of dementia and the quality of life of the patients and reduce the burden on relatives. In this population, slowing the cognitive decline may not be the primary objective of physical activity.

On the other hand, depression, poor physical performance, malnutrition and behavioural disturbances are all linked to faster cognitive decline. In the REAL FR study, an abnormal one-leg balance predicts a higher rate of cognitive decline. Thus, in addition to the prevention and management of complications of the disease, physical activity may also be a realistic approach to delaying cognitive decline.[25,37] It seems reasonable to assume that physical activity in demented patients improves bowel movements and the appetite, some psychological factors (sleep, agitation and mood) and physical performance (balance, gait or strength). These effects may finally result in better cognitive functioning.

Large RCTs in AD patients are scarce, but most report significant improvements in psychological performances and mobility (Table 77.2). In a meta-analysis performed by Heyn *et al.*, it was shown that even in people with cognitive impairment or dementia, exercise training improves behavioural disturbances, physical function and cognitive function.[37] The mean time of most training programmes to achieve these results was less than 4 months. Even a programme including low-intensity physical activity may improve cognitive reserve in AD patients. It is very unlikely that physical activity reverses the pathophysiological process of dementia during this lapse of time. On the other hand, in this very sedentary population, especially in institutions, even a small amount of physical activity radically changes their way of life. In institutions, demented residents spent only 12 min a day in any constructive activity other than watching television.

Current RCTs on AD and physical activity have been short-duration trials with small samples of participants and left many questions unresolved. They need to be replicated in large future RCTs. Moreover, in most of these trials, physical activity was part of a combined intervention such as physical activity plus sensory environmental stimulation, behaviour management or social interaction. The impact of physical training on improved physical health, mood or functional mobility is then impossible to ascertain.

Table 77.2 Randomized controlled trials on physical activity in nursing-home demented residents.

First author	No. of residents	Mean MMSE	Intervention	Summary of major findings in the physical activity group
Molloy, 1988[38]	15	24/30	Light aerobic training 45 min once per week over 2 weeks	Modest improvement of word fluency
Friedman, 1991[39]	30	Moderate to severe	Walking 30 min 3 times per week over 10 weeks	Improvement of communication performances
Mulrow, 1994[40]	194	21/30	Strength, balance, transfer, mobility exercise 45 min 3 times per week over 16 weeks	Modest mobility benefits
Fiatarone, 1994[41]	100	22/30	Resistance training or nutritional supplementation or both, 45 min 3 times per week over 10 weeks	Improved physical performance and muscle mass
Tappen, 42[42]	42	6/30	Skill training 150 min 5 times per week over 20 weeks	Functional improvement
Alessi, 1995[43]	65	14/30	Sit-to-stand, walking and transferring exercise 120 min 5 times per week or rowing and walking 60 min 3 times per week over 9 weeks	Improved mobility, no improvement in sleep disruption
McMurdo, 1995[44]	55	15/30	Seated exercise 45 min twice per week over 6 months	Improved quadriceps strength, no change in cognitive function
Schnelle, 1995[45]	76	12/30	Functional incidental training (FIT) 30–55 min 5 times per week over 8 weeks	Reduced agitation, improved endurance and physical activity
MacRae, 1996[46]	37	20/30	Walking 30 min 5 times per week over 12 weeks	Improved endurance and walking distance
Lazowski, 1999[47]	68	–	Functional for Long Term Care (FFLTC) programme 45 min 3 times per week over 4 months	Improved mobility, balance, flexibility, lower extremities strength
Alessi, 1999[48]	29	13/30	Daytime aerobic exercise plus night-time intervention to decrease noise over 14 weeks	Improved sleep and decreased agitation
Tappen, 2000[49]	65	11/30	Walking or walking + conversation 30 min 3 times per week over 16 weeks	More compliance and less functional mobility decline in the walking + conversation group
Schnelle, 2002[50]	256	12/30	Incontinence care and exercise 60 min 5 times per week over 8 months	Improved continence and physical performance
Van de Winckel, 2004[51]	15	13/30	Physical activity + music 30 min per day over 3 months	Improved MMSE, no effect on behaviour
Stevens, 2006[52]	75	9–23/30	Physical activity 30 min 3 times per week over 12 weeks	Slower cognitive and disability decline
Williams, 2007[53]	90	10/30	Walking plus strength, balance, flexibility exercises 30 min 5 times per week over 16 weeks	Positive effect on mood
Rolland, 2007[4]	134	9/30	Collective exercise (walking, strength, balance and flexibility) 60 min twice per week over 12 months	Slower functional decline, increased gait speed
Dechamps, 2010[3]	160	16/30	Tai chi programme (4 times 30 min per week) or a cognition–action programme (30–45 min twice per week) over 6 months	Slowing of the decline in health-related quality of life based on activities of daily living and neuropsychiatric inventory

Table 77.3 Suggested rules for physical activity programme for demented patients in a nursing home.

Organize a physical activity committee
Identify leaders and organize a physical activity committee for exercise in the nursing home (occupational therapist, physiotherapist, nurse, nurse aids, geriatrician, nursing home director, caregiver, family, animation, volunteers, others)
Be aware that organizing an exercise programme takes effort and planning
Define the outcomes of the exercise programme and the role of each member
Organize a tracking system of the physical activity programme (adherence, side or adverse events, falls)
Organize education training for the staff about the benefits of physical activity in older people with dementia
Plan to buy few foam-rubber groundsheets, cones, easy to grasp soft balls and hoops
Schedule the nursing home physical activity programme
Adjust the sessions of physical activity to the schedule of the nursing home
Plan session of 1 h during the afternoon, twice per week, separated by at least 2 days (it is effective and realistic, but more frequent sessions would probably be better)
Define groups of residents
Inform the staff, the patients and their relatives
Define exercise groups according to their baseline physical performance scores, MMSE score and behaviour disturbances and the affinity between participants
Groups may be between 2 and 10 individuals
Improve adherence
Make the programme enjoyable and accessible
Begin at light intensity and gradually increase over the first month of the programme
Try the music during the sessions
Organize individualized exercises
Give favour to the participants' behavioural readiness for the proposed programme. Add a meaning to exercise in relation to everyday actions
Assess the physical performances of the residents before and regularly during the exercise programme (for example, gait speed, one-leg balance, short physical performance test)
Ritualize the session (same place, people, music, organization)
Finish the session by a snack time
Walking trail may pass the room of each exerciser to encourage joining the group
Inform (balance risks/benefits) and involve the family
Ensure that the intervention will be safe (comorbidities, architecture of the facility, shoes and behaviour disturbances between the residents)
Prescribe hip protectors if needed
Define an exercise programme
Define an inside (and/or an outside) circular walking trail in the nursing home (using the same trail to improve confidence) and an area dedicated to the exercise session
Define an organization to prepare (walking shoes) and group the participants
Duration of the session may be different between the participants
Start by a stretching warm-up
Subjects are encouraged to walk fast to reach moderate breathlessness but not exhaustion. Walking is required for at least half of the session
The walk can be interspersed with strength, flexibility and balance training (predetermined stations along the trail where guardrails in the corridor or foam rubber ground sheets can be used for safety)
Provide fun instructions that participants can enjoy
Encourage communication between the residents and staff during the session
Adapt strength training to the participant and focus on lower extremity strength (squatting at different levels or repeated standups from a chair, lateral elevation of the legs in a standing position and rising on the toes)
Flexibility (imitate simple flexibility exercises demonstrated by the therapist)
Balance training (adapted tai chi exercises, small step trial exercises using cones and hoops on the ground and one- or two-leg balance exercises on the ground or on foam-rubber groundsheets if possible)
Propose easy-to-remember movements that are repeated during training sessions and from one session to another
Adapt the programme as changes occur
Encourage the family to walk with the resident during their visit
Provide memory aides such as visual cues to remember to do the exercises

Physical activity training ranges from 150 min five times per week to 20 min three times per week. Population-based studies differ in terms of age, cognitive impairment severity or type of dementia and outcomes of the trial. Most studies have been organized in nursing home facilities and few in the community (Table 77.2). Only one clinical RCT of exercise for community-dwelling individuals with dementia has been reported.[54] This study involved 153 individuals and their family caregivers. Participants were assigned to an exercise and behaviour management treatment programme. The physical activity programme consisted in an individualized programme of walking, strength training, balance and flexibility exercises. Post-test, the exercisers had better physical functioning and fewer depressive symptoms than the control group. At 24 months, the exercisers were less likely to have been institutionalized.

Practical clinical applications: physical activity for demented patients

It is difficult to propose, on the basis of the literature, a specific kind of physical programme for AD patients. However, intensive exercise programmes may not be practical in some nursing-home settings in the long term. Simple programmes such as an aerobic exercise, twice per week, have been reported to slow the progression of the disease in nursing-home residents. Most RCTs suggest that aerobic exercise such as walking may promote cognitive and functional capacities in people with AD.

Compliance is another key issue for physical activity programmes. In this population, compliance seems to be a major limitation, more than cognitive status. The physical programme has to be enjoyable and accessible. Individualized exercises, based on the participant's behavioural readiness for the proposed training, and music during the session seem to increase compliance. Successful and safe interventions including strength, flexibility and balance training have been reported in this frail and cognitively impaired population. Compliance with the physical activity programme appeared better when the staff assigned to this task communicated with the resident at the same time.

Table 77.3 lists suggested rules for physical activity programme for demented patients in a nursing home.

Conclusion

In addition to its cardiovascular benefits, physical activity may also slow cognitive decline and the incidence of dementia. No RCTs have yet demonstrated that regular physical activity prevents dementia, but increasing evidence suggests that an easy to perform physical activity programme can result in a healthy ageing brain. This argument may convince sedentary individuals to change their lifestyle habits. During AD and dementia, physical activity can slow the rapid functional decline and improve the quality of life of the patient. This approach should be systematically proposed as a key non-pharmacological treatment for this population.

Key points

- Risk factor modification is an important part of dementia prevention.
- Sustained aerobic exercise in mid-life may have a role in preventing cognitive decline.
- Prevention of other risk factors for functional decline may also have benefits in reducing cognitive problems in later life.

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CHAPTER 78

Drug development and Alzheimer's disease

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Introduction

Alzheimer's disease (AD) mainly affects elderly individuals. Because of the ageing of populations worldwide, this disorder is reaching epidemic proportions, with a large human, social and economic burden. The progressive degeneration of neurons in AD causes abnormalities of the systems of neurotransmitters, and a combination of cholinergic and glutamatergic dysfunction appears to underlie the symptomatology of AD. Current drugs for AD target cholinergic and glutamatergic neurotransmission. Cholinesterase inhibitors (ChEIs) and/or butyrylcholinesterase are widely prescribed as symptomatic treatments for AD. Donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl) were approved by the US Food and Drug Administration (FDA) for the treatment of mild to moderately severe AD in 1996, 2000 and 2001, respectively. The use of donepezil for the treatment of severe AD has already been approved in the USA. Memantine [Ebixa and Axura (Europe) and Namenda (USA)] was approved in 2002 by the European Agency for the Evaluation of Medical Products (EMEA) for the treatment of moderately severe to severe AD and in 2003 by the FDA for the treatment of moderate to severe AD.

However, the effects of these treatments are limited or controversial as they do not modify disease progression.[1] Currently, much effort is directed towards identifying disease-modifying therapies. The use of biomarkers of plasma, cerebrospinal fluid (CSF) or neuroimaging [magnetic resonance imaging (MRI) and positron emission tomography (PET)] could play an important role in estimating their efficiency and their potential disease-modifying effect.

This chapter discusses general classes of potential disease-modifying drugs under investigation for the treatment of AD, and also the contribution of the non-pharmacological approach. Compounds and studies selected for this review were identified by systematic searches using PubMed. Only publications in English were reviewed. The ClinicalTrials.gov (http://www.clinicaltrials.gov) website was used for information on ongoing randomized controlled trials (RCTs).

Impact on cholinergic deficit

The mainstays of current pharmacotherapy for AD are compounds aimed at increasing the levels of acetylcholine (ACh) in the brain, thereby facilitating cholinergic neurotransmission through inhibition of the cholinesterases. Other drugs that can increase the ACh levels in brain include ACh precursors, muscarinic agonists and nicotinic agonists.

Recent reports suggest that AChEIs could affect the underlying disease processes[2,3] through neuroprotective and disease-modifying properties.[4] Huperzine A is a selective AChEI with potential properties that include modification of β-amyloid (Aβ) peptide processing, reduction of oxidative stress, neuroprotection and regulation of nerve growth factor (NGF) expression.[5,6] Clinical trials of its derivative, ZT-1, have demonstrated an improvement in cognitive function of AD patients.[7] Phenserine, a derivative of physostigmine, has a dual mode of action: AChEI and inhibitor of the formation of Aβ precursor protein (APP).[8,9] Phenserine is dose-limited in animals by its cholinergic actions. The (+)-phenserine enantiomer (Posiphen), which has weak activity as an AChEI and is potent on Aβ levels and amyloid processing, can be dosed much higher,[10,11] but clinical trials are required. Butyrylcholinesterase may play a role in attention, executive function, emotional memory and behaviour. Furthermore, butyrylcholinesterase activity progressively increases as the severity of dementia advances, whereas acetylcholinesterase activity declines. Therefore, inhibition of butyrylcholinesterase may provide additional benefits.[12] Structural analogues of phenserine,

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cymserine and bisnorcymserine, proved to be potent inhibitors of human butyrylcholinesterase in comparison with phenserine.[13,14] *Salvia officinalis* (sage), which has cholinergic properties, is also under clinical investigation for AD.

Several M1 receptor agonists, such as Lu 25–109 (a compound that directly stimulates muscarinic cholinergic receptors), have been tested in clinical trials without much success.[15] Recent studies which suggest the role of muscarinic agonists in regulating the production of Aβ again raise the possibility that selective M1 agonists could be useful in AD.[16] The M1 muscarinic agonists are neurotrophic, elevate the nonamyloidogenic APP *in vitro*, decrease Aβ levels *in vitro* and *in vivo* and restore cognitive impairments in animal AD models.[17,18]

Nicotinic acetylcholine receptors (nAChRs), which are essential for learning and memory, are reduced in AD brains and research implicates a role for nAChRs in neuroprotection. Targeting nAChRs is an attractive therapeutic approach and several selective ligands for nAChRs have been developed, but a challenge has been the reduction of side effects.[19–22] ABT-089, a selective neuronal nicotinic receptor modulator which shows positive effects in rodent and primate cognitive models,[23] is a candidate for further evaluation as a treatment for AD.[24] GTS-21 (DMXBA) is a selective agonist of alpha7 nicotinic receptors which enhances a variety of cognitive behaviours in mice, monkeys, rats and rabbits. It also displays neuroprotective activity *in vitro* and has shown promising characteristics during phase 1 clinical tests.[25] Ispronicline (TC-1734, AZD-3480) is a selective neuronal nicotinic agonist that is neuroprotective *in vitro* and exhibits memory-enhancing properties *in vivo*. Ispronicline also had a beneficial effect on cognition in subjects with age-associated memory impairment in a phase 2 trial.[26] Other nicotinic agents under clinical evaluation are summarized in Table 78.1.

Anti-amyloid therapies

AD drug development is driven mainly by the amyloid hypothesis. In fact, currently available evidence strongly supports the position that the initiating event AD is related to abnormal processing of β-amyloid (Aβ) peptide, ultimately leading to the formation of Aβ plaques in the brain.[27] This process occurs while individuals are still cognitively normal. After a lag period, which varies from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes. Anti-amyloid agents target production, accumulation, clearance or toxicity associated with Aβ peptide.

Drugs to promote Aβ clearance

Active and passive immunizations were developed to inhibit generation of toxic Aβ aggregates and to remove soluble and aggregated Aβ.

Active immunization

Active immunization of APP transgenic (Tg) mice before they had amyloid plaque deposits resulted in significantly reduced amyloid deposits and neuritic pathology, and Aβ immunization of older mice with pre-existing plaques also resulted in a reduction in plaque pathology. This suggests that this approach is able to slow the progression of amyloid deposition and even reverse it.[28] Subsequent studies have shown that Aβ immunization can also prevent or improve learning deficits in AD Tg mice.[29,30] A phase 1 human trial using an active immunization strategy against Aβ was promising but the phase 2a immunization trial with a synthetic Aβ peptide called AN-1792 was stopped after reports of meningoencephalitis in 6% of the treated patients.[31] The first analysis of efficacy in this trial, reported for a small subset of patients, was suggestive of a slowing cognitive decline, particularly in patients generating the highest antibody titres.[32] A more recent and complete analysis of all treated patients demonstrated no significant efficacy except in the small subset of subjects who had CSF examinations, CSF tau was decreased in antibody responders versus placebo subjects ($p < 0.001$).[33] Immunization strategies research in Tg mouse models has been refocused to establish safer therapeutic approaches.[34] A new generation of AD vaccines has been designed to try to prevent the induction of Aβ reactive T cells, which is thought to have been critical in AN-1792 failure.[35]

Passive immunization

It is also possible to bypass the immune response by direct administration of anti-Aβ antibodies with a passive immunization approach. This approach seems to be as effective as active immunization in Tg mice[36] and could potentially eliminate toxic T-cell-mediated responses to Aβ. In preclinical studies, passive immunization of APP Tg mice with pre-existing evidence of cerebral amyloid angiopathy resulted in an increased severity and incidence of microhaemorrhages, but the physiological implications of these findings remain unclear.[37,38] Antibodies against the β-secretase cleavage site of the APP are another way to limit APP processing. They inhibit Aβ formation *in vitro* and their long-term administration to Tg mice improved cognitive functions associated with a reduction in brain inflammation and incidence of microhaemorrhage.[39] Classical human immunoglobulin (Ig) preparation can also be investigated as a passive

Table 78.1 Ongoing clinical research on new drugs (based on ClinicalTrials.gov website)[a].

Agent/drug	Title	Outcome measures	Reference	Condition	Start date–completion date	Sponsor	Phase
Cholinergic agents							
Nicotinic modulator: MEM-3454	A Study of RO5313534 as Add-on to Donepezil Treatment in Patients with Mild to Moderate Alzheimer's Disease	ADAS-Cog, CANTAB tests, MMSE, ADCS CGIC, Behave-AD-FW, ADCS-ADL, Zarit Burden interview, AEs, laboratory parameters, suicidal risk, concomitant medications, physical and neurological examinations	NCT00884507	AD	May 2009–July 2011	Hoffmann-La Roche	2
EVP-6124	Safety and Cognitive Function Study of EVP-6124 in Patients with Mild to Moderate Alzheimer's Disease	ADAS-cog-13	NCT01073228	AD	April 2010–October 2010	EnVivo Pharma-ceuticals.	2
Antiamyloid agents							
Active immuniza-tion/V950	A Study of V950 in People with Alzheimer Disease	General safety and tolerability after each dose and throughout the study; immunogenicity after each dose and throughout the study	NCT00464334	AD	April 2007–February 2012	Merck	1
Active immuniza-tion/CAD106	Safety, Tolerability and Abeta-specific Antibody Response of Repeated i.m. Injections of Adjuvanted CAD106 in Mild Alzheimer Patients	Safety and tolerability assessments (physical/neurological examinations, ECG, vital signs, standard and special laboratory evaluations, MRIs, AE/SAE monitoring)	NCT01097096	AD	March 2010–?	Novartis	2
Active immunization/ ACC-001	A Long-Term Extension Study Evaluating ACC-001 with QS-21 in Subjects with Mild to Moderate Alzheimer's Disease	Incidence and severity of treatment-emergent adverse events; clinically important changes in safety assessment results including adverse events, vital signs, weight, clinical laboratory tests, ECGs, MRI scans and physical and neurological examinations.; Change from baseline levels of anti-A-beta IgG, anti-A-beta IgM and IgG subclass antibody levels at selected time points	NCT00960531	AD	July 2010–July 2014	Wyeth	2
Active immunization/ UB-311	Study to Evaluate Safety, Tolerability and Immunogenicity of Vaccine in Subjects with Alzheimer's Disease	To evaluate safety and tolerability of the vaccine	NCT00965588	AD	February 2009–December 2010	United Biomedical	1

(*continued overleaf*)

Table 78.1 (*continued*).

Agent/drug	Title	Outcome measures	Reference	Condition	Start date–completion date	Sponsor	Phase
Active immunization/AFFITOPE AD02	Clinical- and Immunological Activity, Safety and Tolerability of Different Doses/Formulations of AFFITOPE AD02 in Early Alzheimer's Disease	Cognitive (ADAS-cog modified) and functional (ADCS-ADL modified)	NCT01117818	Early AD, (based on episodic memory deficit and hippocampal atrophy)	May 2010–April 2012	Affiris	2
Passive immunization/monoclonal antibody GSK933776A	A Clinical Study to Assess Single and Repeat Doses of a New Medication (GSK933776) in Patients with Alzheimer's Disease	AE. Changes suggesting potential adverse events detected in the physical and neurological examination, brain MRI, cognitive status, laboratory parameters, ECG and vital signs; Plasma pharmacokinetic parameters. Pharmacodynamic effects. CSF detectable levels. Effects on plasma and CSF biomarkers. Titre and neutralizing activity. Exploratory PET scan	NCT00459550	AD	March 2007–November 2010	GlaxoSmithKline	1
Passive immunization/monoclonal antibody PF-04360365	Multiple IV Dose Study of PF-04360365 in Patients with Mild to Moderate Alzheimer's Disease	Safety/tolerability in subjects with mild to moderate AD dosed for 18 months. (AE, physical/neurological examinations, vital signs, 12-lead ECG, clinical laboratories, brain MRI, cognitive assessments); pharmacokinetics following administration of multiple doses in subjects with mild to moderate AD. ADAS-cog, DAD, plasma/CSF Aβ, CSF tau and phosphotau, CSF protein, RBCs, WBCs and glucose, immunogenicity (anti-drug antibodies)	NCT00722046	AD	May 2010–August 2011	Pfizer	2
Passive immunization/monoclonal antibody PLY2062430 (solanezumab)	Effect of LY2062430 on the Progression of Alzheimer's Disease	ADAS-Cog, ADCS-ADL, CDR-SB, NPI, volumetric MRI, MMSE, RUD-Lite, EQ-5D Proxy, QoL-AD, change from baseline to end point in plasma LY2062430 to investigate a relationship between plasma LY2062430 and plasma Aβ levels, change from baseline to end point in plasma Aβ	NCT00904683	AD	May 2009–September 2012	Eli Lilly	2

Passive immunization/monoclonal antibody AAB-001 (bapineuzumab)	Study Evaluating the Efficacy and Safety of Bapineuzumab in Alzheimer Disease Patients	ADAS-Cog, DAD, Neuropsychological Test Battery, CDR	NCT00667810	AD	May 2008 – June 2014	Elan Pharmaceuticals	3
Passive immunization/monoclonal antibody MABT5102A	A Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Anti-Abeta in Patients with Alzheimer's Disease	Safety and tolerability of single and multiple doses of MABT5102A	NCT00736775	Mild to moderate AD	August 2008–?	Genentech	1
Passive immunization/monoclonal antibody R1450 (gantenerumab)	A Multiple Ascending Dose Study of R1450in Patients with Alzheimer Disease	AEs, laboratory parameters, vital signs. Pharmacokinetic parameters of R1450 in plasma	NCT00531804	AD	December 2006–?	Hoffmann-La Roche	1
α-Secretase activator bryostatin-1	Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics Study of Bryostatin 1 in Patients with Alzheimer's Disease	AEs, ADAS, CIBIC, CDR, ADCS-ADL, SIB, Hopkins Verbal Learning Test – Revised, temperature, respiratory rate, blood pressure, heart rate, ECG, physical examination, haematology, blood chemistry, urinalysis, pharmacokinetics, protein kinase C activity (pharmacodynamics)	NCT00606164	AD	April 2008–December 2008	Blanchette Rockefeller Neurosciences Institute	2
β-Secretase inhibitor thiazolidinedione, rosiglitazone	Rosiglitazone Effects on Cognition for Adults in Later Life	Cognitive measures: delayed list recall, Stroop Interference Test. Biological outcomes: plasma insulin, IDE, Aβ-40, Aβ-42, inflammatory cytokines and F2-isoprostanes. MRI outcome: whole brain and medial temporal lobe atrophy rate. Cognitive measures: ADAS-cog total score, story recall verbal fluency, paired associate learning, SOPT, rating scales	NCT00242593	MCI	June 2006–July 2010	GlaxoSmithKline	2
γ-Secretase inhibitor LY450139	Effects of LY450139, on the Progression of Alzheimer's Disease as Compared with Placebo	ADAS-Cog. ADCS-ADL, CDR, NPI, RUD-Lite, EQ-5D Proxy, Qol-AD, MMSE, a chemical marker of AD in the blood which may be lowered by LY450139, FDG-PET, vMRI, AV-45-PET, CSF tau, safety, to measure levels of LY450139 and their effect on safety, chemical markers and effectiveness	NCT00762411	AD	September 2008–March 2012	Eli Lilly	3

(*continued overleaf*)

Table 78.1 (*continued*).

Agent/drug	Title	Outcome measures	Reference	Condition	Start date–completion date	Sponsor	Phase
γ-Secretase inhibitor BMS-708163	Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of BMS-708163	Safety assessments will be based on adverse event reports and the results of vital sign measurements, ECGs, physical examinations and clinical laboratory tests	NCT01079819	AD	April 2010–July 2010	Bristol-Myers Squibb	1
γ-Secretase modulator CHF-5074	Safety, Pharmacokinetics and Pharmacodynamics Study of Treatment with CHF 5074 in Healthy Young Male Subjects	AEs	NCT00954252	Young healthy male volunteers	October 2009–December 2009	Chiesi Pharmaceuticals	1
Anti-aggregation and anti-fibrillization agents ELND005 (AZD-103)	ELND005 Long-Term Follow-up Study in Subjects with Alzheimer's Disease	Safety and tolerability analyses will be based on the frequency and severity of AEs and on clinically important changes in laboratory assessment results	NCT00934050	AD	June 2009–April 2011	Elan Pharmaceuticals	2
Epigallocatechin-3-gallate (EGCg)	Sunphenon EGCg (in the Early Stage of Alzheimer's Disease) (SUN-AK)	ADAS-Cog	NCT00951834	Early stage of AD (Diagnosis DSM-IV and NINCDS/ADRDA, Dubois criteria 2007)	November 2009–April 2011	Charite University, Berlin	2
NIC5-15	Development of NICS-15 in the Treatment of Alzheimer's Disease	Pharmacokinetic analysis, safety assessments including vital signs, physical examination, symptom checklist, complete blood count, serum chemistries, urinalysis, ECG, ADAS-Cog	NCT00470418	AD	January 2007–March 2010	Department of Veterans' Affairs	2
Tau aggregation inhibitor							
Nicotinamide	Safety Study of Nicotinamide to Treat Alzheimer's Disease	ADAS-Cog	NCT00580931	AD	January 2008–January 2011	University of California	2
Neuroprotective agents							
Vitamin E and memantine (TEAM-AD)	A Randomized, Clinical Trial of Vitamin E and Memantine in Alzheimer's Disease	ADCS/ADL	NCT00235716	AD	August 2007–July 2012	Department of Veterans' Affairs	3
Docosahexaenoic acid (DHA)	Lipoic Acid and Omega-3 Fatty Acids for Alzheimer's Disease	ADL, ADAS-Cog	NCT01058941	AD	April 2010–April 2013	Oregon Health and Science University	1-2

EGB 761 (*Ginkgo biloba* extract)	Effect of EGb761® on Brain Glucose Metabolism in Three Groups of Elderly with Memory Complaint, Mild Alzheimer's Disease, and Cognitively Normal	18FDG-PET, change in brain atrophy; incidence of AEs	NCT00814346	Cognitive impairment, AD	October 2008–June 2012	Ipsen	2
T-817 MA (benzothiophene derivative)	Efficacy and Safety of T-817 MA in Patients with Mild to Moderate Alzheimer's Disease	ADAS-cog; secondary objectives are to evaluate the safety ADCS-ADL and ADCS-CGIC	NCT00663936	AD	April 2008–September 2011	Toyama Chemical	2
Resveratrol supplement	Randomized Trial of a Nutritional Supplement in Alzheimer's Disease	ADAScog, CGIC	NCT00678431	AD	January 2008–June 2011	Department of Veterans' Affairs	3
Curcumin	Efficacy and Safety of Curcumin Formulation in Alzheimer's Disease	To determine if curcumin formulation affects mental capacity in Alzheimer's patients based on mental examinations; to determine if curcumin formulation changes blood concentrations of Aβ	NCT01001637	AD	October 2009–November 2010	Jaslok Hospital and Research Centre	2
Neurorestorative factors							
Neurotrophic growth factor: CERE-110	Randomized, Controlled Study Evaluating CERE-110 in Subjects with Mild to Moderate Alzheimer's Disease	ADAS-Cog, Neuropsychological Test Battery, MMSE, NPI, ADCS-ADL	NCT00876863	AD	September 2009–July 2012	Ceregene	2
NsG0202	Encapsulated Cell Biodelivery of Nerve Growth Factor to Alzheimer's Disease Patients	AEs	NCT01163825	AD	January 2008–December 2011	NsGene	1
Other treatments							
Hormone therapy SERMs: raloxifene	Raloxifene for Women with Alzheimer's Disease	ADAS, CDR, ADCS-ADL, NPI, cognitive subscale of the Alzheimer's Disease Assessment Scale, other cognitive tests (East Boston Memory Test, digit ordering, category fluency, Trail Making Test, Boston Naming Test short version, MMSE, narrative writing, semantic binding), caregiver burden interview	NCT00368459	AD	August 2006–July 2010	National Institute on Aging	2

(*continued overleaf*)

Table 78.1 (*continued*).

Agent/drug	Title	Outcome measures	Reference	Condition	Start date–completion date	Sponsor	Phase
Hormone therapy: testosterone (Androgel 1%)	Hormone and Information Processing Study	Behavioural and mood measure: Profile of Mood States (POMS), cognitive changes measured by neuropsychological tests: ADAS-Cog (MCI version), route test, paragraph recall, CSF, APOE genotyping	NCT00539305	MCI, AD	July 2009–June 2012	Solvay Pharmaceuticals	3
5-HT 6 receptor antagonist: SB-742457	A Study of SB-742457, Added to Donepezil for the Treatment of Mild-to-moderate Alzheimer's Disease	Change in cognition and function after 24 weeks, change in cognition and function after 12, 24, 36 and 48 weeks, safety and tolerability, pharmacokinetics and exploratory pharmacogenetics	NCT00710684	Mild-to-moderate AD	July 2008–December 2010	GlaxoSmithKline	2
5-HT 6 receptor antagonist: SAM-531	Study Comparing 3 Dosage Levels of SAM-531 in Outpatients with Mild to Moderate Alzheimer Disease	ADAS-Cog; they include the changes from baseline to week 24 in the DAD and in the NPI, ADCS-CGIC, CANTAB and the responder rate at week 24	NCT00895895	AD	April 2009–June 2011	Wyeth	2
Selective histamine H3 receptor antagonist: GSK239512	Study to Evaluate the Efficacy and Safety of GSK239512 in Alzheimer's Disease	Change from baseline in composite score of Cogstate battery; Change from baseline in ADAS-Cog total score at weeks 8 and 16; CIBIC+ score at weeks 8 and 16; safety measures: AEs, 12-lead ECG, vital signs (systolic and diastolic blood pressure, heart rate), clinical laboratory evaluations	NCT01009255	AD	November 2009–January 2011	GlaxoSmithKline	1
Anti-histamine agent: Dimebon	Safety and Efficacy Study Evaluating Dimebon in Patients with Mild to Moderate Alzheimer's Disease on Donepezil	ADCS-ADL, ADAS-Cog, CIBIC-plus, NPI, RUD-Lite, EQ-5D	NCT00829374	AD	March 2009–December 2011	Medivation	3
PF-04447943 in phase 2 (phosphodiesterase 9A inhibitors)	A Study of PF-04447943 Compared to Placeboin Subjects with Mild to Moderate Alzheimer's Disease	ADAS-Cog	NCT00930059	AD	September 2009–September 2010	Pfizer	2

RAGE inhibitor: TTP488 (PF 04494700)	A Phase 2 Study Evaluating the Efficacy and Safety Of PF 04494700 in Mild to Moderate Alzheimer's Disease	Evaluate the efficacy of PF 04494700 relative to placebo. Change from baseline in a standardized cognitive measure after 18 months of treatment. Examine the safety and tolerability of PF 04494700 relative to placebo. AEs, vital signs, physical examination, neurological examination, 12-lead ECG, laboratory tests (haematology, blood chemistry, urinalysis) and brain MRI. Evaluate the effects of PF 04494700 on potential biomarkers of RAGE inhibition and amyloid imaging (AV-45, F18 PET). Evaluate the potential dose response of PF 04494700. Evaluate the pharmacokinetics and characterize the pharmacokinetic/pharmacodynamic relationship of PF 04494700 to potential biomarkers and relevant efficacy and safety end points	NCT00566397	AD	December 2007–March 2011	Pfizer	2

[a]Magnetic resonance imaging (MRI); adverse event/serious adverse event (AE/SAE); Alzheimer's disease (AD); mild cognitive impairment (MCI); electrocardiogram (ECG); cerebrospinal fluid (CSF); positron emission tomography (PET); Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog); Disability Assessment for Dementia (DAD); Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL); Clinical Dementia Rating-Sum of Boxes (CDR-SB); Neuropsychiatric Inventory (NPI); Mini Mental State Examination (MMSE); Resource Utilization in Dementia-Lite (RUD-Lite); EuroQol 5-Dimensional Health-related Quality of Life Scale Proxy version (EQ-5D Proxy); Quality of Life in Alzheimer's Disease (QoL-AD); Clinician's Interview Based Impression of Change (CIBIC); Severe Impairment Battery (SIB).

immunization therapy in AD, as a small percentage of antibodies are directed against Aβ peptide sequences. Intravenous infusion of Igs in five AD patients over a 6 month period prevented further cognitive decline,[40] suggesting that this approach could potentially act like a passive immunotherapy. Human trials of passively administered anti-Aβ antibodies are now being initiated. Other antibodies have recently reached clinical evaluation: GSK933776A, PF-04360365, PLY2062430 (solanezumab) and AAB-001 (bapineuzumab) (Table 78.1). In a recent RCT that enrolled patients with mild-to-moderate AD, treatment with bapineuzumab for 78 weeks reduced cortical 11C-PiB retention compared with both baseline and placebo.[41]

Drugs to reduce Aβ production

α-Secretase activators

APP processing by α-secretase is a non-amyloidogenic pathway, because the α-secretase cleavage site is within the Aβ sequence of APP. Enhanced cleavage at this site may represent a potential disease-modifying strategy. Bryostatin 1, a macrolide lactone, exhibits high affinity for protein kinase C and dramatically enhances the secretion of the α-secretase product in patients' fibroblasts[42] (Table 78.1). Etazolate (EHT-0202), a selective GABA receptor modulator, stimulates neuronal α-secretase and increases sAPPα production.[43] This drug, which is orally bioavailable, has recently been tested in a phase 2 RCT in patients with mild-to-moderate AD (NCT00880412, results not available). Talsaclidine, an M1 agonist that stimulates the non-amyloidogenic α-secretase processing *in vitro* and decreases CSF Aβ in AD patients following chronic treatment,[44,45] holds potential disease-modifying properties.

β-Secretase inhibitors

β-secretase has been shown to be a transmembrane aspartic protease, β-site Aβ cleaving enzyme 1 (BACE1). BACE-1 processing of Aβ precursor protein is the first step in the pathway leading to the production of Aβ. BACE-1 knockout mice develop normally and appear to have completely abolished Aβ production.[46] A selective BACE-1 inhibitor, GSK188909, reduced levels of secreted and intracellular Aβ40 and Aβ42 *in vitro* and also in APP transgenic mice brains.[47] Thiazolidinediones also act as β-secretase inhibitors by stimulating peroxisome proliferator-activated receptor-γ (PPARγ). PPARγ agonists, such as rosiglitazone, also have anti-inflammatory effects.[48,49] Thiazolidinediones are under evaluation in AD, but recent data have shown a potential higher risk of myocardial infarction with these compounds.[50] To compensate for the brain's reduced ability to use glucose in AD, administration of ketone bodies or their metabolic precursors such as medium-chain triglycerides (MCTs) might be another strategy. In a preliminary study with 20 subjects with AD or mild cognitive impairment (MCI), single doses of MCTs demonstrated pharmacological activity and significant efficacy in cognitive performance.[51] A phase 2b clinical trial in AD patients confirmed ketone bodies' safety and efficacy on cognition. A pivotal phase 3 clinical trial in AD patients is planned.[52]

γ-Secretase inhibitors and modulators

Inhibition of γ-secretase targets the generation of Aβ42, but other proteins are also substrates of this enzyme and particularly the transmembrane Notch receptor, involved in vital functions.[53–55] Abnormalities in the gastrointestinal tract, thymus and spleen in animal models result from inhibition of Notch cleavage.[56,57] Preclinical studies established that γ-secretase inhibitors can reduce brain Aβ and reverse Aβ-induced cognitive deficits in transgenic mice. LY450139 dihydrate, a γ-secretase inhibitor, inhibits Aβ formation *in vitro* and *in vivo*. In phase 1 volunteer studies, a dose-dependent reduction in plasma Aβ was demonstrated. However, Aβ concentrations were unchanged in CSF.[58,59] In an RCT of AD patients treated with LY450139 dihydrate, Aβ40 decreased significantly in plasma and decreased in a non-significant manner in CSF.[60] Single doses of GSI-953, a selective γ-secretase inhibitor, also produced dose-dependent reductions of plasma but not CSF Aβ peptides in humans.[61] Tarenflurbil is the pure *R*-enantiomer of flurbiprofen and is the first in a novel class of selective Aβ-42-lowering agents. It modulates γ-secretase and is highly specific for its effects on Aβ-42 and, unlike the γ-secretase inhibitors, does not interfere with the function of Notch. In a phase 2 study, tarenflurbil was well tolerated for up to 24 months of treatment in 210 AD patients, with evidence of a dose-related effect on measures of daily activities and global function in patients with mild AD,[62] but a phase 3 clinical trial was negative. Table 78.1 gives an overview of drugs that are currently in research and development in this field.

Anti-aggregation and anti-fibrillization agents

An alternative approach to secretase inhibition, which raises the problem of interfering with normal enzymatic reactions, is to inhibit Aβ aggregation into neurotoxic oligomers. Tramiprosate (NC-531 or 3APS) is a glycosaminoglycan mimetic that binds to Aβ and inhibits amyloid plaque formation.[63] Preclinical data have shown that tramiprosate reduces brain and plasma levels of Aβ and prevents fibril formation.[64] In a phase 2 trial, long-term administration of tramiprosate was safe, well tolerated and reduced CSF Aβ-42 levels in patients with AD. Tramiprosate has reached phase 3 clinical trials.[65] However, a phase 3 trial in the USA was negative and was stopped in Europe. Dysregulation of cerebral metal ions (Fe^{2+}, Cu^{2+} and Zn^{2+}) and their interactions with Aβ may contribute to AD by playing a role in the precipitation

and cytotoxicity of Aβ.[66] Metal ions are required for Aβ protein oligomerization and recent studies showed that metal chelators could produce a significant reversal of Aβ deposition *in vitro* and *in vivo*.[67] XH1 and DP-109, both metal chelators, attenuated Aβ pathology in APP Tg mice.[68,69] Clioquinol (PBT-1) is a Cu/Zn chelator that promotes Aβ dissolution. In a pilot phase 2 clinical trial in AD patients, this fibrillization inhibitor shows a significant efficacy in the more severely affected group according to the authors[70] but this point is discussed.[71] Another chelator, desferioxamine, has shown some benefit in AD, but also severe adverse effects.[72] PBT-2, another metal protein-attenuating compound, was tested in a phase 2 trial in patients with early AD. PBT-2 affects the Cu^{2+}-mediated and Zn-mediated oligomerization of Aβ protein. The safety profile was favourable. Cognitive efficacy was restricted to two measures of executive functioning. The effect on putative biomarkers for AD in CSF but not in plasma was suggestive of a central effect of the drug on Aβ metabolism.[73] Another compound interfering with the aggregation and fibrillization of Aβ, ELND005 (AZD-103), is under evaluation in a clinical trial (Table 78.1).

Drugs to target tau protein

Microtubule-associated protein (MAP) tau is abnormally hyperphosphorylated in AD. Several kinases are reported to phosphorylate tau *in vitro*, including glycogen synthase kinase-3 (GSK-3), cyclin-dependent kinase-5 (CDK-5), mitogen-activated protein kinase family members (MAPK), casein kinase, calcium calmodulin-dependent kinase II, protein kinase A and others. Some of them, such as GSK-3, could be also involved in Aβ generation, promoting cell death, production of inflammatory molecules and cell migration.[74] Phosphoseryl/phosphothreonyl protein phosphatase-2A (PP-2A), which is co-localized with tau and microtubules in the brain, is apparently the most active enzyme in dephosphorylating the abnormal tau to a normal-like state.[75] Other phosphatases have also been implicated.[76] Reducing abnormal phosphorylation and restoring or stimulating phosphatase activity are promising therapeutic strategies. Lithium reduces tau phosphorylation *in vitro*, promotes microtubule assembly through inhibition of GSK-3[77] and has been shown to reduce tau phosphorylation in APP Tg mice.[78] In a preliminary clinical trial of lithium in AD patients, no effect of lithium on tau and Aβ-42 in the CSF was observed, which does not support the notion that lithium may lead to reduced hyperphosphorylated tau in AD after short-term treatment.[79] Methylthioninium chloride (Trx0014) has been shown *in vitro* to prevent aggregation of tau into tangles. It has demonstrated cognitive and behavioural benefits in animal models.[80]

Neuroprotective agents

Another alternative approach involves protection against cellular damage caused by oxidative, inflammatory or other toxic stressors.

Antioxidants

Genetic and lifestyle-related risk factors for AD could be associated with an increase in oxidative stress, suggesting that oxidative stress is involved in the early stage of the pathology.[81] Individuals with MCI or very mild AD show increased levels of lipid peroxidation and nucleic acid oxidation in postmortem brain and plasma.[82] Free radicals and oxidative injury to neurons could chronologically precede Aβ plaque deposition and tau phosphorylation.[83] Several antioxidants that have been investigated for their potential to reduce the risk of AD include vitamins A, C and E, coenzyme Q, selenium and polyunsaturated fatty acids. Vitamin E had been show to slow progression of the disease in patients with moderately severe AD.[84] However, recent meta-analysis and trial results suggest that vitamin E increases morbidity and mortality[85] and a Cochrane review does not support the use of vitamin E to treat AD.[86] The lack of consistent efficacy data for vitamin C and its questionable safety could also discourage its use.[87] Most of the published epidemiological studies are consistent with a positive association between high reported omega-3 polyunsaturated fatty acid consumption and a lower risk of developing cognitive decline or AD later in life.[88] Docosahexaenoic acid (DHA) is the most abundant omega-3 fatty acid in the brain. DHA acts in the brain via neurotrophic and anti-apoptotic pathways. In addition, DHA may act through anti-neuroinflammatory pathways, as DHA possesses anti-inflammatory properties in the periphery. The results from the first randomized, double-blind, placebo-controlled clinical trial evaluating the effects of dietary omega-3 fatty acid supplementation on cognitive functions in patients with mild to moderate AD showed no significant efficacy of daily intake of DHA and eicosapentaenoic acid. However, in a subgroup of patients with very mild cognitive dysfunction [Mini Mental State Examination (MMSE) >27 points], a significant reduction in MMSE decline rate was observed in the omega-3 fatty acid-treated group compared with the placebo group.[89] α-Lipoic acid (LA), an essential cofactor in mitochondrial dehydrogenase reactions, functions as an antioxidant and reduces oxidative stress.[90] LA seems to exert a cellular protective effect as evidenced by decreases in apoptotic markers in fibroblasts from AD patients.[91] Clinical preliminary data show that LA might be a successful therapy for AD.[92] EGb761, a *Ginkgo biloba* extract that has free radical scavenging properties, inhibits the formation of Aβ fibrils, attenuates mitochondrion-initiated apoptosis and decreases the activity of caspase-3, a key enzyme

in the apoptosis cell signalling cascade.[93] Mitoquinol, an antioxidant that targets mitochondrial dysfunction, has demonstrated encouraging preclinical results. Mitoquinol mimics the role of the endogenous mitochondrial antioxidant coenzyme Q10 and augments its antioxidant capacity to supraphysiological levels.[94] Melatonin, an indolamine secreted by the pineal gland, may also protect neuronal cells from Aβ-mediated toxicity via antioxidant properties and could attenuate tau hyperphosphorylation.[95] Isoflavones are also under clinical evaluation for their antioxidant properties (Table 78.1). Other clinical trials with antioxidants are on the way (Table 78.1).

Anti-inflammatory drugs

Laboratory evidence shows that inflammatory mechanisms contribute to neuronal damage in AD. Epidemiological evidence[96] suggests that non-steroidal anti-inflammatory drugs (NSAIDs) may favourably influence the course of the disease. In a 1993 trial, indomethacin appeared to protect AD patients from cognitive decline, according to the authors,[97] but this point of view is not shared by Cochrane reviewers.[98] Another trial with indomethacin failed to show any efficacy in the progression of AD.[99] Ibuprofen, celexocib, rofecoxib and naproxen did not slow the progression of AD.[100–102] In a phase 2 AD clinical trial with (*R*)-flurbiprofen, a few subsets of patients who had high blood concentrations of this drug demonstrated a benefit in cognitive and behavioural performance.[103] However, Myriad Genetics has discontinued the development of (*R*)-flurbiprofen (Flurizan or MPC-7869). Cyclophosphamide is a potent anti-inflammatory and immunomodulatory drug acting primarily by inhibiting the proliferation of immune cells.[104] Excess tumour necrosis factor-alpha (TNF-α) has been shown to mediate the disruption in synaptic memory mechanisms caused by Aβ in addition to its proinflammatory functions.[105] Etanercept, an antagonist of TNF-α, delivered by perispinal administration in AD patients, showed great potential in a pilot study. Among traditional medicine products, resveratrol, a component of grapes, berries and other fruits, is a polyphenol that has been shown to mediate its effects through modulation of many different pathways. For instance, resveratrol has been shown to reduce the expression of inflammatory biomarkers and induce antioxidant enzymes.[106] Lastly, curcumin, a polyphenolic molecule safely used as a food colouring, proved to be immunomodulatory and has shown Aβ-40 aggregation inhibition properties *in vitro* and *in vivo*.[107]

Glutamate-mediated neurotoxicity

The glutamatergic system has long been recognized for its role in learning and memory and recent studies indicate the involvement of glutamate-mediated neurotoxicity in the pathogenesis of AD.[108,109] The neurotransmitter glutamate activates several classes of receptors and especially three major types of ionotropic receptors: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and *N*-methyl-D-aspartate (NMDA). Chronic activation of receptors, in particular of the NMDA type, ultimately leads to neuronal damage. Complete NMDA receptor blockade has also been shown to impair neuronal plasticity. Thus, both hypo- and hyperactivity of the glutamatergic system lead to dysfunction. Memantine is an uncompetitive NMDA receptor antagonist and has been approved for the symptomatic treatment of AD. Most other centrally acting NMDA antagonists have been discarded because of severe adverse psychomimetic and cardiovascular effects. A series of second-generation memantine derivatives are currently under development and may have greater neuroprotective properties than memantine. Neramexane is a new NMDA receptor antagonist that is currently under development. *In vivo*, neramexane enhances long-term spatial memory in adult rats.[110] Its clinical development seems to be completed. Another mode of action is the positive modulation of AMPA receptors.[111] LY404187, a selective positive modulator of AMPA receptors, improved the performance of cognitive function in animal models.[112] LY451395, an AMPA receptor potentiator, administered to AD patients did not show a statistically significant difference in effect versus placebo on cognitive functions in a clinical trial.[113] CX516 (Ampalex) enhances brain activity by positive modulation of AMPA receptors.

Neurorestorative approaches

NGF promotes survival and differentiation of neurons and neurotrophic factors have been suggested as contributors to AD pathophysiology. In rhesus monkeys, ageing is associated with a significant reduction in cortical cholinergic innervation, but this reduction is reversible by NGF delivery to cholinergic somata in the basal forebrain.[114] Phenotypic knockout of NGF activity in transgenic anti-NGF mice results in a progressive neurodegenerative AD-type phenotype and the neurodegeneration induced by the expression of anti-NGF antibodies can be largely reversed by NGF delivery.[115] A phase 1 trial evaluated NGF gene delivery in eight individuals with mild AD, by implanting autologous fibroblasts genetically modified to express human NGF into the forebrain. The results suggested improvement in the rate of cognitive decline after a mean follow-up of 22 months.[116] AIT-082 (Neotrofin) increases levels of NGF and stimulates nerve sprouting in the brain. A phase 1 study of AIT-082 was conducted in 36 mild AD patients with no significant side effects.[117] Growth factor modulators are also under clinical development for AD treatment (Table 78.1).

Animal studies show that human neural stem cells transplanted into animal brains differentiated into neural cells and significantly improved the cognitive functions. Neural stem cell grafts present a potential strategy of treatment. This raises the possibility of stimulating inherent precursor cells to replace lost neurons.[118,119]

Other potential therapeutic strategies

Hormonal therapy

RCTs suggest a very limited effect of estrogens on attention and verbal performance when administered to postmenopausal women with AD.[120] The efficacy of selective estrogen receptor modulator (SERMs) that exert tissue-specific estrogenic effects has also been investigated in AD RCTs (Table 78.1). It also appears that estrogens may work in conjunction with gonadotropins, such as luteinizing hormone (LH). LH, which can modulate cognitive behaviour, is present in the brain and has one of the highest receptor levels in the hippocampus.[121] It has been suggested that the increase in gonadotropin concentrations, following menopause, could be one of the causative factors for the development of AD.[122] The reduction in neurodegenerative disease among prostate cancer patients who are frequently treated with gonadotropin-releasing hormone (GnRH) agonist supports the role of LH and GnRH in AD.[122] Testosterone supplementation may also benefit cognitive function in men with AD.[123] In healthy older men, short-term testosterone administration enhances cognitive function.[124] Among other hormonal compounds, insulin-like growth factor-1 (IGF-1) is supposed to increase clearance of Aβ. Preliminary evidence shows that the growth hormone secretagogue MK-677 (ibutamoren mesylate), a potent inducer of IGF-1 secretion, could improve cognitive function in cognitively impaired patients.[125] However, MK-677 was ineffective at slowing the rate of progression of AD in a clinical trial.[126] Excessive levels of corticosteroid have been associated with impaired attention, concentration and memory and *in vivo* studies suggest that prolonged exposure to high circulating levels of glucocorticoid may be associated with a faster progression of AD.[127] Mifepristone is a glucocorticoid receptor antagonist and could improve cognition in AD. Pilot trials in patients with AD provide data on the safety and feasibility of this approach, but more extensive studies are needed.[128]

Drugs to target mitochondrial dysfunction

Attention and short-term memory-enhancing effects of H3 receptor antagonists are well described. Dimebon is a molecule previously approved in Russia as a non-selective antihistamine. The molecular mechanism by which Dimebon exerts its effects is not known, but the most potent pharmacological activities established *in vivo* is the stabilization of mitochondrial membrane depolarization in the setting of molecular stress and neurite outgrowth, which may be a consequence of its mitochondrial action. Dimebon has been shown to bind with high potency to serotonin (5-HT6 and 5HT-7) and α-adrenergic receptors (subtypes 1A, 1B, 1D, 2B), both implicated in cognitive pathways. Binding to histamine receptors is not believed to play a role in its therapeutic activity. Dimebon demonstrated cognition-enhancing properties *in vivo* and in a human pilot clinical trial in AD.[129] In a randomized, double-blind, placebo-controlled study,[130] patients showed significant improvements for five outcome measures, including assessment of cognition (ADAS-cog and MMSE), function (ADCS-ADL) and behaviour (NPI). It showed a significant drug–placebo difference in change from baseline on the ADAS-cog at week 26 which was not driven by worsening in the placebo group as patients given Dimebon were improved from their baseline values. The difference observed in the clinician- assessed global function scale (CIBIC-plus) supports the clinical relevance of this effect.

Statins

Epidemiological evidence suggests that statins may reduce the risk of developing AD. The mechanism of this putative protective effect is not completely understood, but may be related to the relationship between elevated cholesterol and amyloid deposition. Amyloidogenic APP processing may also occur preferentially in the cholesterol-rich regions of membranes known as lipid rafts. A placebo-controlled 1 year study of atorvastatin calcium showed a positive effect on decline on the ADAS-cog compared with placebo at 6 and 12 months follow-up in 63 patients with AD.[131] In *post hoc* analysis of a placebo-controlled study, simvastatin significantly decreased Aβ-40 levels in the CSF of patients with mild AD.[132] A major phase 3 study of atorvastatin[133] was negative.

Receptor for advanced glycation end product inhibitors

The receptor for advanced glycation end products (RAGE) is a cell-bound receptor of immunoglobulin which may be activated by a variety of pro-inflammatory ligands including advanced glycation end products leading to secretion of cytokines, which may link the amyloid pathway to the inflammatory pathway.[134] RAGE-mediated inflammation caused by glial cells and subsequent changes in neuronal glucose metabolism are likely to be important contributors to neurodegeneration in AD.[135] These pathways are

considered interesting drug targets for the treatment of AD. RAGE inhibitor: TTP488 (PF04494700) is now under clinical development (Table 78.1).

Others

Recent studies have suggested modifications of serotonin cerebral metabolism in MCI and AD. Lecozotan (SRA-333), a selective serotonin 1a receptor antagonist, was developed for the treatment of AD after promising results in animal studies.[136] On the other hand, xaliproden (SR57746A), a 5-HT1a receptor agonist which appears either to mimic the effects of neurotrophins or to stimulate their synthesis, has reached phase 3, but its development is over. Both monoamine oxidase (MAO) A and MAO B have been implicated in AD pathogenesis and rasagiline, an MAO B inhibitor which exhibits neuroprotective and anti-apoptotic activity *in vitro* and *in vivo*,[137] is under clinical evaluation. Antihypertensive medications are associated with a lower incidence of AD and some of them as angiotensin-converting enzyme inhibitors or calcium channels blockers have become a source of interest. A phase 2 clinical trial in AD with MEM 1003, the (+)-enantiomer of a dihydropyridine, that has been optimized for central nervous system activity, is planned (Table 78.1). Blood levels of homocysteine may contribute to AD pathophysiology by vascular and direct neurotoxic mechanisms. Even in the absence of vitamin B deficiency, homocysteine levels can be reduced by administration of high-dose supplements of vitamin B. However, in a recently published RCT trial, high-dose B vitamin supplements failed to show any effect in cognitive decline in AD. Folate deficiency also induces an imbalance of sadenosyl-L-methionine (SAM) which could have an impact on cognitive functions. Dietary supplementation with SAM in the absence of folate attenuated these consequences *in vivo*.[138] Other agents are also under evaluation and Table 78.1 gives an overview of the drugs that are currently in research and development.

Non-pharmaceutical therapies

Several studies are ongoing to evaluate the impact of cognitive intervention (NCT00646269, NCT00319891) and physical activity (NCT00403507, NCT01061489, NCT01128361) on the memory and cognitive abilities of patients diagnosed with AD. The approach based on the transcranial or deep brain stimulation seems promising.

Repetitive transcranial magnetic stimulation (rTMS) to the prefrontal cortex could improve language performance in patients with AD.[139] Although the mechanisms of rTMS-induced naming facilitation in these patients are unknown, the procedure may be worth testing as a novel approach to the treatment of language dysfunction. This procedure seems to have persistent beneficial effects on sentence comprehension in AD patients. rTMS in conjunction with other therapeutic interventions (drug or cognitive brain training), may represent a novel approach to the treatment of cognitive dysfunction in AD patients (NCT01168245, NCT01179373). Several studies are ongoing to assess the ability of rTMS with H2 coil to prefrontal and parieto-temporal cortex (NCT00753662) to improve cognitive performance in patients with AD.

Fornix/hypothalamus deep brain stimulation (DBS) could modulate neurophysiological activity in these pathological circuits and possibly produce clinical benefits. In a phase 1 trial in six patients with mild AD, they received continuous DBS for 12 months.[140] DBS drove neural activity in the memory circuit, including the entorhinal and hippocampal areas, and activated the brain's default mode network. PET scans showed an early and striking reversal of the impaired glucose utilization in the temporal and parietal lobes that was maintained after 12 months of continuous stimulation. Cognitive evaluation (ADAS-Cog and MMSE) suggested possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients. Modulating pathological brain activity in AD with DBS merits further investigation. Several studies are ongoing to evaluate DBS with bilateral electrode implantation in the nucleus basalis Meynert (NCT01094145) and in the fornix/hypothalamus (NCT00888056).

Prevention and AD

Because no effective curative approaches are available, preventive approaches in the field of AD are needed. Indeed, because AD is a slowly progressing and age-dependent disease, delaying onset by as little as 5 years could halve the number of people afflicted with the illness.[141]

Epidemiological data suggest a preventive effect of EGb 761 in AD,[142] but RCT results evaluating EGb 761 for the treatment of AD are contradictory. The aim of the GuidAge Study is to evaluate the efficacy of 240 mg per day of EGb 761 in the prevention of AD.[143] Previous studies suggested that many factors may be involved in the occurrence of AD at late ages. Because of the probable multifactorial nature of AD, it seems logical to initiate multidomain interventions to examine their potential synergistic effects. The Multidomain Alzheimer Preventive Trial (MAPT) is an ongoing study which aims to evaluate the efficacy of a multidomain intervention (nutritional, physical and cognitive training) and omega-3 treatment in the prevention of cognitive decline in frail elderly persons aged 70 years or over.[144]

The PREADVISE study is trying to establish whether taking selenium and/or vitamin E supplements can help to prevent memory loss and dementia such as AD (NCT00040378). Other ongoing trials are assessing the

effects of antihypertensives on individuals at risk for AD (NCT00980785) and simvastatin on CSF AD biomarkers in cognitively normal subjects (NCT01142336).

Conclusion

AD is an increasingly important issue in our societies. Many clinical studies are ongoing with numerous new compounds, but still no disease-modifying drug is available at present. To explain the disappointing results of several RCTs, researchers have highlighted different errors, both in drug choice and development programmes. Indeed, because of the complexity of AD, it is clear that multi-target therapies could be the future treatment approach. Multi-target therapies[145] can be designed in several ways. (1) The most conventional strategy is to prescribe several individual drugs. This approach is already used in AD, where ChEIs can be given together with NMDA receptor antagonists for better symptomatic effects. (2) Another strategy is to develop drugs that contain two or more active ingredients delivered in the same device. (3) The third strategy is to design a single compound with selective polypharmacology. Drugs such as memoquin (ChEI, β-secretase inhibitor, Aβ anti-aggregant, antioxidant properties and decreases tau hyperphosphorylation), talsaclidine (M1 agonist, α-secretase) and M-30 (monoamine oxidase inhibitor, antioxidant and iron-chelating properties and modulation of APP processing) are now in preclinical stages of testing.

A majority of the recent drugs under evaluation seem to act on multiple targets. The pharmacological field needs to be explored carefully, specifically with regard to new drug tolerability and security of use. Therefore, it needs to be shown that the benefits of such treatments outweigh the risk of side effects before they can be recommended for patients with AD. The publication of negative data is also an important issue and could enlighten researchers' ability to improve their knowledge about drug actions.

Key points

- Although a great deal of progress has been made with our understanding of the pathophysiological processes in involved in Alzheimer's Disease (AD), there has been little advancement in the use of effective disease-modifying agents.
- The mainstays of current pharmacotherapy for AD are compounds aimed at increasing the levels of acetylcholine (ACh) in the brain.
- It is clear that multi-target therapies could be the future for effective treatment approaches.

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CHAPTER 79

Other dementias

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Introduction

Dementia is an acquired syndrome in which there is impairment of cognitive abilities, severe enough to interfere with the individual's occupational, social and functional abilities. As conventionally used, the term dementia implies 'degenerative' and 'progressive', but it is also often used in the context of static conditions (such as post-stroke cognitive impairment) or reversible conditions (such as depression or medication-related cognitive impairment). Table 79.1 provides a list of the many causes of dementing illnesses that can occur in older individuals.

Because Alzheimer's disease (AD) is widely reported as the commonest cause of dementia worldwide, it may be tempting for clinicians to make this diagnosis routinely without systematically considering alternative or additional diagnoses. Such a practice, although probably fortuitously correct most of the time, would fail to detect reversible diseases that affect cognition (which often occur concomitantly with AD) and other non-AD aetiologies that may confer different prognosis and necessitate different treatment modalities from AD.

Population-based studies on Western and Asian cohorts indicate that vascular dementia (VaD) is often the commonest reported dementia aetiology after AD. When actively sought for with standard criteria, the prevalence of dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) may be higher than previously thought. For example, the Islington study of community-dwelling elderly revealed the following distribution of dementia subtypes: AD 31.3, VaD 21.9, DLB 10.9 and FTD 7.8%.[1] Specialized memory clinic-based estimates differ somewhat from population-based studies in having a relatively higher prevalence of non-AD aetiologies and concomitant potentially reversible conditions, especially depression and metabolic abnormalities. Generally, however, only a small percentage of these conditions have been found to be completely reversible, most notably hypothyroidism and vitamin B_{12} deficiency. The prevalence of aetiologies in demented patients presenting to private practitioners has not been estimated, but would likely reflect values intermediate between population- and specialized outpatient-based estimates.

This chapter discusses some conditions that are commonly encountered in clinical practice, notably vascular cognitive impairment and non-AD neurodegenerative dementias. We focus on conceptual advances and clinical gems that can help in the diagnosis and management of these conditions and conclude with a general approach to the evaluation of dementia with parkinsonism.

Vascular cognitive impairment/ vascular dementia

Epidemiological studies in the West indicate that VaD is second in prevalence to AD, accounting for 12–20% of dementia cases. The incidence of VaD increases with age, but much less steeply than AD. Unlike AD, men are disproportionately more affected, especially at younger ages. Earlier international comparative studies revealed a higher frequency of VaD in Asian countries, notably Japan and China. The ratio of AD to VaD varied from 1.4 in Beijing, China, to 2.8 in Korea, compared with the ratio of 3.4 in Europe. However, a recent study from China reported a higher prevalence of AD than VaD (3.5 versus 1.1%) in the population older than 65 years.[2] Whether this portends an epidemiological shift towards Western trends or is due to methodological differences is unclear.

Despite being described by Alois Alzheimer more than a century ago, the role of cerebrovascular disease (CVD) in dementia has been dogged by misconception. For the greater part of the twentieth century, it was commonly held that the most frequent cause of late-onset dementia was arteriosclerosis. Seminal work in the late 1960s challenged this assumption, establishing that the main type of pathology underlying late-onset dementia was degenerative and of Alzheimer type rather than vascular. This led to

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 79.1 Causes of dementia other than Alzheimer's disease.

1 Other degenerative dementias
  a Dementia with parkinsonism
    i Diffuse Lewy body disease
    ii Parkinson's disease dementia
    iii Progressive supranuclear palsy
    iv Corticobasal degeneration
    v Multiple system atrophy
  b Frontotemporal dementia
  c Huntington's disease
  d Hallervorden–Spatz disease
  e Kufs' disease
2 Vascular dementia
3 Other CNS causes
  a Normal-pressure hydrocephalus
  b Epilepsy
  c Traumatic dementia
    i Acute and chronic subdural haematoma
    ii Dementia pugilistica
    iii Craniocerebral injury
  d Tumours
    i Primary CNS tumours: gliomas, meningiomas
    ii Metastatic tumours, lymphoma, leukaemia
    iii Paraneoplastic limbic encephalitis
4 Psychiatric disorders
  a Depression
  b Others: schizophrenia, mania, other psychoses
5 Inflammatory
  a Cerebral vasculitis
    i Primary angiitis of the CNS
    ii Part of systemic involvement: disseminated lupus erythematosus, temporal arteritis, Behçet's disease, Wegener's granulomatosis, Churg–Strauss disease
  b Multiple sclerosis
6 Metabolic
  a Endocrinopathies
    i Hyper- and hypothyroidism
    ii Glucose disorders: hyper- and hypo- states
    iii Cushing's disease
    iv Addison's disease
  b Electrolyte abnormalities
    i Hypo- and hypernatraemia
    ii Hypercalcaemia
  c Inherited
    i Wilson's disease
    ii Mitochondrial disorders
    iii Adult lysosomal diseases (particularly metachromatic leukodystrophy)
    iv Peroxisomal disorders
7 Nutritional deficiency
  a Thiamine deficiency
  b Vitamin B_{12} deficiency
  c Folate deficiency
  d Vitamin B_6 deficiency (pellagra)

(*continued overleaf*)

Table 79.1 (*continued*).

8 Infective
  a Neurosyphilis
  b Human prion disease
  c HIV-associated dementia
  d Progressive multifocal leukoencephalopathy
  e Post-meningitic/post-encephalitic dementia
9 Drugs (remembered by the mnemonic ACUTE CHANGE IN MS[30])
  a **A**ntiparkinsonian drugs
  b **C**orticosteroids
  c **U**rinary incontinence drugs
  d **T**heophylline
  e **E**mptying (motility) drugs
  f **C**ardiovascular drugs
  g **H**2 blockers
  h **A**ntimicrobials
  i **N**SAIDs
  j **G**eropsychiatric drugs
  k **E**NT drugs
  l **I**nsomnia drugs
  m **N**arcotics
  n **M**uscle relaxants
  o **S**eizure drugs
10 Toxins
  a Alcohol
  b Heavy metals: lead, aluminium, mercury
  c Carbon monoxide poisoning
11 Others
  a Obstructive sleep apnea
  b Whipple's disease
  c Neurosarcoidosis

a redefinition of late-onset dementia as primarily the result of AD, with the result that the nosological status of vascular dementia became uncertain.

The field moved forward when the concept of *multi-infarct dementia* (MID) was described to reflect dementia due to multiple large and small strokes. The field further evolved with the recognition that MID was just one of many subtypes of VaD (Table 79.2).[3] VaD encompasses several clinicopathological subtypes, ranging from haemorrhagic (including hypertension, cerebral amyloidal angiopathy, subarachnoid haemorrhage, post-haemorrhagic obstructive hydrocephalus, subdural haematoma and haematological causes) to ischaemic and combinations of ischaemia and haemorrhage (such as cortical vein and sinus thromboses). Ischaemic forms of VaD can be further divided into large-vessel, small-vessel and strategic infarct subtypes (Table 79.2). Among the hereditary group, the most extensively studied condition is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetically transmitted small-vessel disorder that has

Table 79.2 Subtypes of vascular dementia (VaD).

Subtype	Description
Multi-infarct dementia (cortical VaD)	Predominantly resulting from large cortical infarcts
Small-vessel dementia (subcortical VaD)	Predominantly resulting from subcortical lacunes, white and/or deep grey matter lesions
Strategic infarct dementia	Resulting from a unilateral or bilateral infarct in a strategic area
Hypoperfusion dementia	Resulting from brain damage due to hypoperfusion
Haemorrhagic dementia	Resulting from intracerebral haemorrhage
AD with CVD	Presence (or presumption on the basis of clinical picture and brain imaging) of both significant Alzheimer and vascular pathology, both of which are thought to contribute to dementia
Hereditary dementia	Genetic causes of VaD, such as CADASIL due to mutation in the NOTCH 3 gene in chromosome 19

Table 79.3 NINDS–AIREN criteria for probable and possible vascular dementia (VaD).[5]

Probable VaD

1 Dementia
2 Cerebrovascular disease
   - Focal neurological signs consistent with stroke
   - Neuroimaging evidence of clinically relevant vascular lesions
3 Temporal relationship between dementia and CVD, as evidenced by one or more of the following:
   - Onset of dementia within 3 months of a recognized stroke
   - Abrupt deterioration
   - Fluctuating or stepwise progression

Clinical features consistent with diagnosis:

- Early presence of gait disturbance
- History of unsteadiness, frequent and unprovoked falls
- Early urinary frequency, urgency and other urinary symptoms not explained by urological disease
- Pseudobulbar palsy
- Personality and mood changes, abulia, depression, emotional incontinence and subcortical deficits, including psychomotor retardation and abnormal executive function

Criteria for relevant cerebrovascular disease on brain imaging

- Topography
  a Large-vessel strokes
  b Extensive white matter change
  c Lacunes (frontal/basal ganglia)
  d Bilateral thalamic lesions
- Severity
  a Large-vessel lesion of dominant hemisphere
  b Bilateral strokes
  c White matter lesions affecting> 25% of white matter

Possible VaD

1 Dementia with focal neurological signs but without neuroimaging confirmation of definite CVD
2 Dementia with focal signs but without a clear temporal relationship between dementia and stroke
3 Dementia and focal signs but with subtle onset and variable course of cognitive deficits

Alzheimer's disease with cerebrovascular disease

1 Clinical criteria for possible AD
2 Clinical and imaging evidence of CVD

been mapped to chromosome 19q12 with mutations in the Notch 3 gene.

To make a diagnosis of VaD, three elements are necessary: presence of dementia, presence of cerebrovascular lesions and a temporal relationship between the two. Traditional diagnostic criteria for VaD can be broadly divided into two groups.[4] The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), and the *Classification of Mental and Behavioural Disorders*, 10th Revision, under the International Classification of Diseases (ICD-10), are general diagnostic tools that outline criteria without operationalizing them. The second set, such as the widely used National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN) criteria (Table 79.3),[5] is a development of the first two and offers operational criteria. Autopsy studies have shown that although these criteria are generally able to exclude about 90% of AD, they have only modest sensitivity (50–70%) in diagnosing VaD. There is a tendency to misclassify mixed dementia (AD with CVD) as VaD (54% for ADDTC and 29% for NINDS–AIREN), especially in the 'possible VaD' category. Application of the NINDS imaging criteria also did not distinguish between demented and non-demented patients.

Advances in the past decade have consolidated our understanding of the contribution of CVD in cognition in three key areas.[6] First, *vascular cognitive impairment (VCI)* is a more comprehensive and appropriate concept than VaD. VCI is an umbrella term that includes VCI-no dementia, VaD and mixed dementia (Figure 79.1). About 5% of VCI people over the age of 65 are estimated to have VCI; in patients under 74, VCI may be the single most common cause of cognitive impairment.[7] The inclusion of VCI-no dementia, a subset with less severe cognitive impairment that do not meet formal criteria for dementia, is analogous to the concept of the pre-dementia stage of amnestic MCI in AD and serves to emphasize the preventable nature of VCI and the importance of early diagnosis. This concept can be taken further: while the progression of VCI is analogous

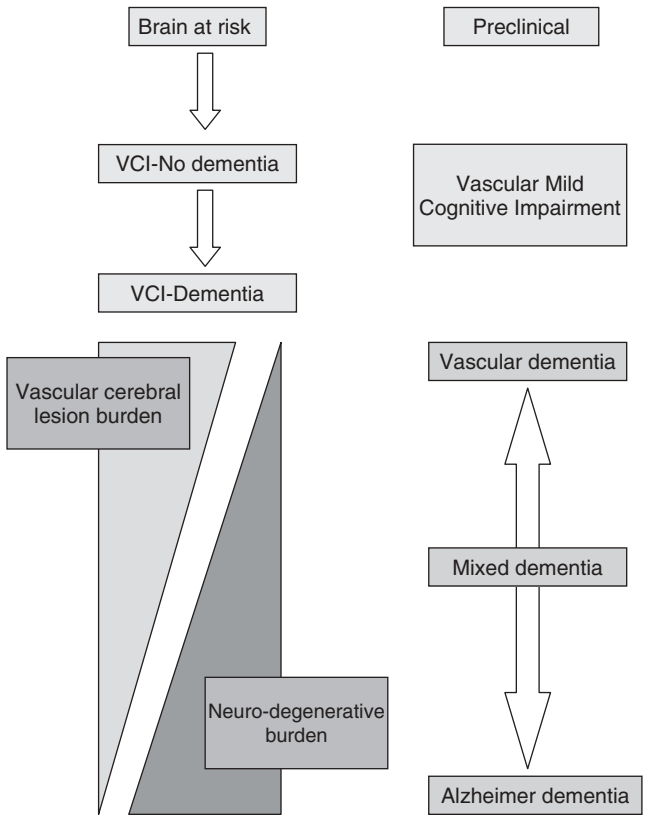

Figure 79.1 Schematic diagram depicting the spectrum of vascular cognitive impairment (VCI) and the overlap between vascular dementia (VaD) and neurodegenerative disease using Alzheimer's disease (AD) as an example. In this conceptual model, AD and VaD fall on a continuous spectrum of disease. The gradient of features, driven by the underlying burden of vascular (lacunes, white matter disease and cerebral microhaemorrhage) and neurodegenerative (amyloid plaques and neurofibrillary tangles) pathology, would then determine the phenotype and nosologic classification (VaD, mixed or AD).

to secondary prevention, primary prevention requires the recognition of the presence of risk factors in an asymptomatic susceptible host, termed 'brain-at-risk'.

Second, with increasing recognition of the overlap between AD and VCI in terms of predisposing factors and pathophysiology, these two disorders are currently conceptualized as a continuous spectrum rather than coexisting unrelated conditions (Figure 79.1).[8] Apart from the ends of the spectrum where pure AD or pure VaD lie, mixed dementia constitutes the majority of patients who cannot easily be classified as being in one group or the other. Limited data suggest that patients with mixed dementia outnumber those with pure AD.[6] Within the mixed group, vascular brain injury acts additively or synergistically with concomitant AD pathology to produce more severe cognitive dysfunction than either process alone. In support of this, clinicopathological data such as the Nun Study indicate that subjects with both vascular disease and AD pathology exhibit either more severe cognitive impairment during life than those with pure AD or require less pathology to produce the same amount of cognitive impairment. This suggests that in AD patients with concomitant CVD, both conditions require treatment, even if the vascular component may appear trivial.

Third, our understanding of the pathophysiology of VCI has evolved to distinguish VCI associated with large vessel disease from that associated with small vessel disease, including subcortical ischaemic vascular disease (SIVD) and non-infarct ischaemic changes such as leukoaraiosis. SIVD includes the lacunar state and Binswanger's disease, characterized, respectively, by multiple lacunes and periventricular leukoencephalopathy that typically spares the arcuate subcortical U fibres. Limited data from clinical samples indicate that SIVD is the most common subtype.[4] A recent study reported that 82.2% had small-vessel VaD whereas only 25.9% had large-vessel VaD.

Although there is some degree of overlap, large-vessel strokes tend to yield a clinical picture of cortical dementia, as opposed to the subcortical dementia of small-vessel forms (Figure 79.2). These can be reasonably differentiated by a combination of cognitive features, neurological features and clinical course (Table 79.4).[9] SIVD typically causes a slow, subacute-onset dementia that is characterized by executive dysfunction, impaired attention and impaired processing speed, with a comparatively milder memory deficit. There may be 'lower-half parkinsonism' producing characteristic gait changes of hesitation, *marche à petit pas* (walking with hurried small steps) and diminished step height. In fact, the triad of dementia, urinary incontinence and gait disturbance, is more often produced by small-vessel VaD than normal-pressure hydrocephalus (NPH). Neuropsychiatric disturbances such as depression, anxiety, agitation, disinhibition and apathy are not uncommon in VaD, especially the small-vessel subtype.

Dementia may occur in 25–33% of ischaemic stroke cases at ages 65 years and older. Predictors of the occurrence of dementia following stroke include older age, lower education level, non-White race, pre-existing cognitive decline, 'silent' infarcts on neuroimaging, ischaemic rather than haemorrhagic strokes, hemispheric rather than brainstem or cerebellar lesions, left rather than right hemispheric lesions, larger and recurrent strokes and more severe neurological deficit on admission. The number of vascular risk factors might be more important for predicting cognitive impairment than any individual factor. Apolipoprotein ε4 has been associated with increased risk for AD and mixed dementia, but not VaD. Leukoaraiosis may be an important predictor of cognitive decline in domains affected by cerebral small-vessel disease. There has been a continuing debate on whether periventricular or deep leukoaraiosis is more damaging to cognition. In the Rotterdam Study,

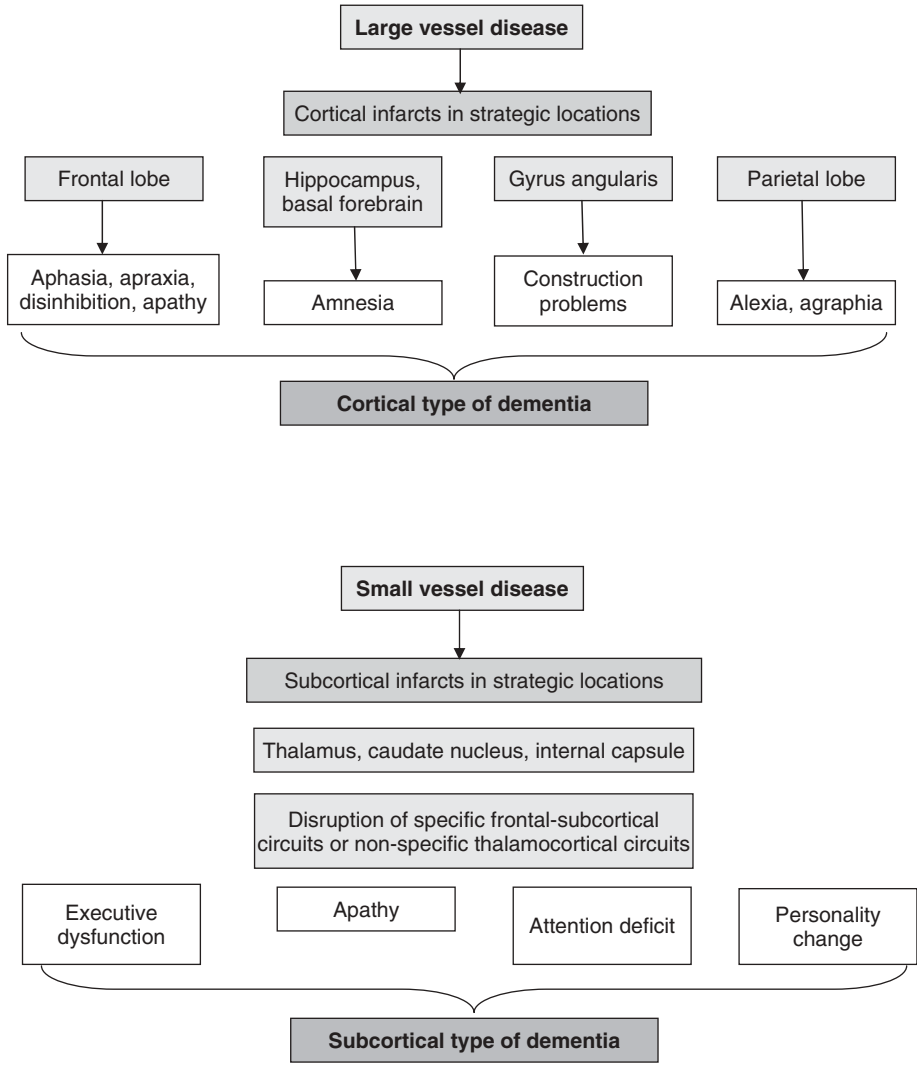

Figure 79.2 Differentiation of clinical features of vascular dementia by vessel size.

periventricular leukoaraiosis and infarcts but not subcortical white matter lesions were correlated with a decline in processing speed and general cognition.[10] The number of cerebral microbleeds as diagnosed by magnetic resonance imaging (MRI) study may be an independent predictor of cognitive impairment and severity of dementia. Patients undergoing coronary artery bypass grafting (CABG) may be at risk for both early (within 1 month) and late (beyond 5 or more years) cognitive decline. A recent observational study suggests that late cognitive decline after CABG is not specific to the use of cardiopulmonary bypass, because nonsurgical cardiac comparison patients also showed mild late cognitive decline.[10]

Management of VaD is multi-pronged and involves (1) symptomatic treatment for cognition, (2) management of neuropsychiatric disturbances, (3) stroke prevention strategies and (4) management of stroke-related disabilities such as spasticity, parkinsonism and incontinence. To date, three studies of donepezil in VaD and two of galantamine (one in VaD, the other in mixed dementia and VaD) have been completed.[7] A modest improvement in cognition analogous to 3 points on the ADAS-Cog has been found, but effects on other outcomes such as activities of daily living, behaviour and global assessment are inconsistent. Two studies in VaD of memantine, an NMDA antagonist that protects against glutamate-mediated excitotoxicity, show modest benefits in cognition, but no benefit on a global outcome measure. Depression is common in association with stroke and SIVD and is an eminently treatable condition; hence a course of antidepressant is justifiable if there is a suspicion of concomitant depression. Levodopa can be helpful in the treatment of apraxic gait in SIVD if the burden of vascular disease lies in the basal ganglia or substantia nigra.

Table 79.4 Characteristics of cortical and subcortical dementia.

Clinical feature	Cortical	Subcortical
Cognitive deficits	Memory impairment prominent	Executive dysfunction prominent
	Heteromodal cortical symptoms	Memory deficit milder
	Neuropsychological syndromes	Perseveration
	Executive dysfunction usually present	Mood changes (depression, emotional lability, apathy)
Neurological symptoms	Field cut	Imbalance/falls
	Lower facial weakness	Gait disturbance
	Upper motor neuron signs	Altered urine frequency
	Dominant/non-dominant lobe signs	Mild upper motor neurone signs
		Dysphagia
		Extrapyramidal signs
Clinical course	Abrupt onset	60%: slow, less abrupt onset
	Stepwise deterioration	80%: slow progression with or without stepwise decline
	Fluctuating course with plateaux	

Strategies for stroke prevention include anticoagulation in patients at risk of cardioembolism, antiplatelet agents, targeting modifiable risk factors (such as hypertension, diabetes, hyperlipidaemia and metabolic syndrome) and optimizing lifestyle factors (such as smoking cessation, physical activity, addressing mid-life obesity and fish consumption). Observational studies suggest a role for vitamin B_{12}, folic acid and homocysteine in VCI, although rigorous intervention studies are lacking.[10] Some studies suggest that treatment of hypertension may reduce the risk of incident dementia, although the recent HYVET-COG study of those aged ≥80 years treated with indapamide with option of perindopril or placebo found no effect on dementia. Despite the benefit of statins in reducing stroke by 30%, this did not translate into benefits in cognition in the PROSPER study.

In the later stages of disease, VaD is often associated with a greater degree of physical, behavioural and functional issues than in AD. The goal of treatment is then shifted to the alleviation of morbidity and caregiver burden and a multidisciplinary team input is often required.

Lewy body disease

There is growing appreciation that dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are actually part of the spectrum of Lewy body disease (LBD).[11] Differences in early disease presentation in DLB and PDD gradually merge into a similar common pathway as the disease progresses, such that they share identical features in the end stage (Figure 79.3). The hallmark of both diseases is the presence of Lewy bodies, which are related to dysregulation of the synaptic protein, α-synuclein and suggest neurobiological links with other synucleinopathies such as multiple system atrophy (MSA). Recent evidence suggests that it is the presynaptic α-synuclein aggregates, rather than Lewy body pathology, that are synapto-toxic and cause neurodegeneration in LBD.

PDD should be used to describe dementia that develops in the context of established Parkinson's disease, whereas a diagnosis of DLB is appropriate when dementia precedes or coincides within 1 year of the development of motor symptoms.[12,13] Within these two 'extremes' of the DLB–PDD spectrum, considerable variation and overlap in disease presentation have been described, for instance, insidious onset of mild parkinsonism and forgetfulness or visual hallucinations early in the course of PD. The likelihood of clinically presenting as 'typical' DLB (Table 79.5) is directly related to the distribution of Lewy body pathology and inversely related to the severity of AD pathology.[12] Three patterns of Lewy body pathology have been described: (1) brainstem-predominant, corresponding to the clinical phenotype of PDD, (2) cerebral cortex-predominant, corresponding to the clinical phenotype of DLB, and (3) transitional pattern, with distribution of Lewy pathology and clinical phenotype intermediate between the other two subtypes. In addition, concomitant AD pathology is also present in 90% of LBD cases (more commonly β-amyloid plaques and, to a lesser extent, neurofibrillary tangles). Compared with those with mild or no neurofibrillary tangle pathology, DLB patients with marked concurrent tangle pathology often present with an insidious amnestic syndrome more suggestive of AD and there are also fewer cognitive fluctuations, fewer neuropsychiatric symptoms and less parkinsonism.[11]

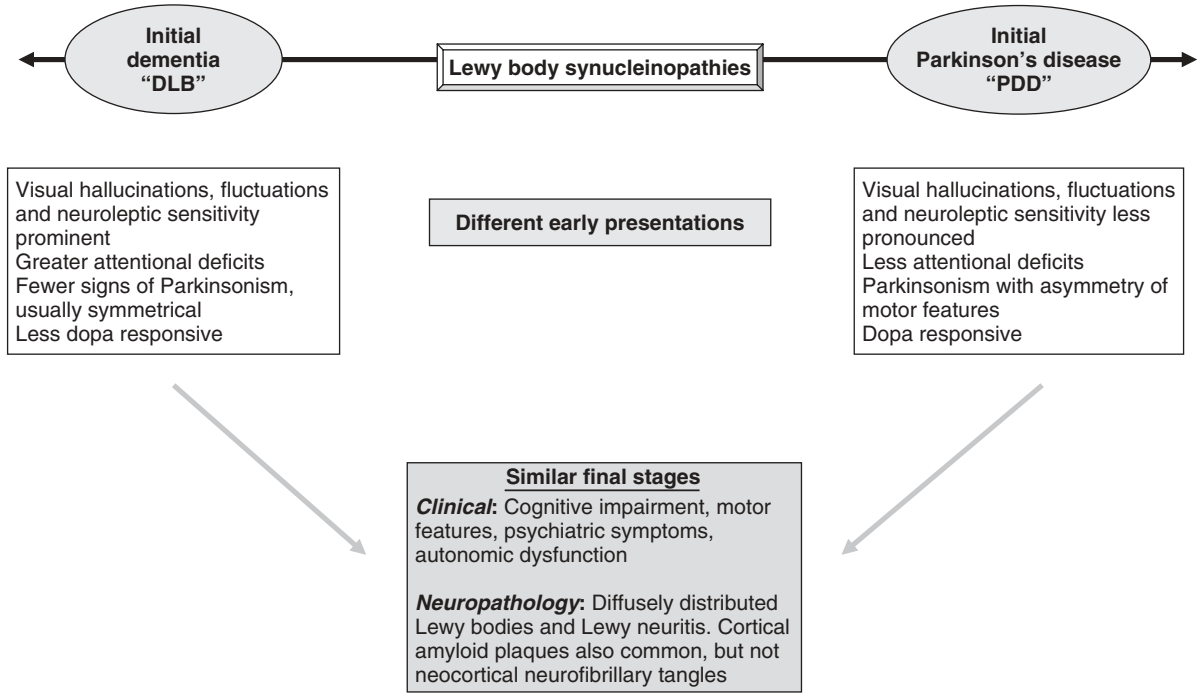

Figure 79.3 Schematic representation depicting how dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) represent different points in the spectrum of Lewy body disease. Although the initial clinical manifestations of DLB and PDD differ, they are often indistinguishable in terms of clinical and neuropathological features by the end stage.

Dementia with Lewy bodies

DLB is now the preferred term for a series of diagnostic appellations that can be found in the older literature, including Lewy body variant of AD, Lewy body dementia, senile dementia of Lewy body type and cortical Lewy body disease. DLB represents the second most common cause of neurodegenerative dementia in older people after AD, accounting for ~15–20% in autopsy series. Onset of DLB is between 50 and 90 years of age and the duration of illness varies between 6 and 10 years.

Clinically, DLB is marked by a progressive dementia syndrome with fluctuating cognition and alertness, recurrent, well-formed visual hallucinations and parkinsonism (Table 79.5). Autopsy validation studies reported that previous criteria for DLB have high specificity (80–100%), but more limited sensitivity (35–80%). The latest consensus criteria were expanded to include suggestive features to address this limitation.[12]

The characteristic neuropsychological profile in early DLB is that of a 'dysexecutive' syndrome with prominent executive, attentional and visuospatial dysfunction. Amnesia may not be prominent or persistent in the early stages, but is usually evident with progression. Extrapyramidal motor symptoms in DLB are present in about 75% and consist primarily of bradykinesia, rigidity and postural instability. Compared with idiopathic Parkinson's disease, resting tremor is less common and, even if present, is never a prominent feature. Responsiveness to levodopa is also less pronounced.

Fluctuations in cognitive performance, attention and level of consciousness are the most characteristic feature of DLB. The marked amplitude between the best and worst performances distinguishes it from the minor day-to-day variations that commonly occur in dementia of any cause. Transient changes of consciousness in which patients are found mute and unresponsive for periods of several minutes may represent the extreme of fluctuation in arousal, but are often mistaken for transient ischaemic attacks despite a lack of focal neurological signs. One study reported that informant endorsement of at least three items out of four composite features of fluctuations (daytime drowsiness and lethargy, daytime sleep of $\geq$2 h, staring into space for long periods, episodes of disorganized speech) yielded a positive predictive value of 83% for DLB against the alternate diagnosis of AD.[14]

Prominent neuropsychiatric symptoms at time of presentation are among the defining features of DLB. Visual hallucinations are typically recurrent, well formed and detailed, and usually involve three-dimensional mute images of people and animals. Caregivers may under-report visual hallucinations, hence patient self-report can be useful. The presence of visual hallucinations is a marker of cortical LB pathology and greater cortical cholinergic deficits and

Table 79.5 Diagnostic criteria for dementia with Lewy bodies (DLB).

Central feature
Progressive cognitive decline with reduced social and occupational function
Core features
Fluctuating cognition with pronounced variations in attention and alertness
Recurrent vivid visual hallucinations
Spontaneous parkinsonism
Suggestive features
REM sleep disorder
Severe neuroleptic sensitivity
SPECT/PET imaging: low dopamine transporter uptake in basal ganglia
Probable DLB: 2 core OR at least 1 core plus 1 suggestive
Possible DLB: 1 core OR 1 suggestive
Supportive features
Repeated falls and syncope
Transient, unexplained loss of consciousness
Severe autonomic dysfunction, e.g. orthostatic hypotension, urinary incontinence
Systematized delusions
Hallucinations of other modalities
Depression
CT/MRI scan: relative preservation of medial temporal lobe structures
SPECT/PET perfusion scan: generalized low uptake with reduced occipital activity
EEG: prominent slow wave activity with temporal lobe transient sharp waves
Features less likely to be present
History of stroke
Any other physical illness or brain disorder sufficient to account for the clinical picture
If parkinsonism appears for first time only at severe stage of dementia

Modified from McKeith *et al.*[12]

predicts a good response to cholinergic therapy. Other common behavioural manifestations include hallucinations in other modalities, depression, misidentifications and systematized delusions. The most common form of delusions in DLB are misidentification delusions (i.e. delusions that someone is in the room, delusions that the home is not one's own or that television or movie personalities are actually present in the home), followed by persecutory/paranoid delusions, phantom boarder delusions (the belief that an unwanted person is living in the house) and abandonment delusions.

Rapid eye movement (REM) sleep behaviour disorder (RBD) is manifested by vivid and often frightening dreams during REM sleep. Because the usual limb atony in REM sleep is lost, patients are able to 'act out their dreams'. They may talk or shout in their sleep, strike out at their bed partner and even fall out of bed. As the patient may have little recall of these episodes, history is obtained from the bed partner. RBD is commonly a very early symptom that precedes the onset of dementia and parkinsonism by many years and, curiously, usually improves as the disease progresses. It is frequently associated with synucleinopathies (DLB, PD and MSA) and only rarely with other neurodegenerative disorders. Thus, a history of RBD, if present, is of great diagnostic utility because RBD can serve as a fairly specific antecedent biomarker of an underlying synucleinopathy.[15]

Approximately 50% of DLB patients do not react adversely to antipsychotic agents, hence a history of neuroleptic tolerance does not exclude a diagnosis of DLB. In contrast, a positive history of severe neuroleptic sensitivity is strongly suggestive. These range from sedation, increased confusion and worsening of parkinsonism, to more deleterious effects such as irreversible parkinsonism, impaired consciousness and marked autonomic disturbances. Autonomic dysfunction may occur early in DLB to produce orthostatic hypotension, urinary incontinence, constipation, impotence and swallowing difficulties. It can also contribute to repeated falls, syncope and transient loss of consciousness.

Differential diagnoses include other dementia syndromes such as AD and VaD, other causes of delirium, other neurological syndromes such as PD, progressive supranuclear palsy or Creutzfeld–Jakob disease and other psychiatric disorders such as late-onset delusional disorders, depressive psychosis and mania. Useful neuroimaging investigations in the diagnosis of DLB include (1) relative preservation of hippocampal and medial temporal lobe volume on MRI, (2) occipital hypoperfusion on SPECT imaging, compared with posterior parietotemporal hypoperfusion in AD, and (3) reduced dopamine transporter uptake in basal ganglia on SPECT/PET (single photon emission computed tomography/positive emission tomography) imaging. A multi-centre study reported the diagnostic utility of a ^{123}I-FP-CIT SPECT scan in the differential diagnosis of probable DLB and AD (sensitivity 78%, specificity 90%).[16] There is preliminary evidence that low α-synuclein levels in the cerebrospinal fluid may be a useful biomarker in the diagnosis of DLB.

Management of DLB involves the treatment of motor, cognitive, psychiatric and autonomic dysfunction. The clinician needs to be mindful of the tension between improving one symptom at the expense of worsening another – for example, aggravating hallucinations with levodopa. In the treatment of neuropsychiatric symptoms, conventional neuroleptic medications are best avoided, while atypical newer agents should be used judiciously. There is evidence that cholinesterase inhibitors (ChIs) are effective and relatively safe for the treatment of psychiatric and cognitive symptoms in DLB, with major side effects (mainly

gastrointestinal) similar to those reported in AD. A recent case report highlighted that DLB patients may be more susceptible to bradyarrhythmic side effects from ChIs due to the associated autonomic dysfunction.[17] Memantine has recently been reported to produce cognitive and global benefits in DLB but without any significant improvement in psychiatric symptoms.[18] However, caution should be exercised as there are case reports of worsening of delusions and hallucinations with memantine use in DLB.

Parkinson's disease with dementia

It is now recognized that prevalence figures of 20–40% from earlier cross-sectional surveys of movement-disorder clinic populations underestimated the frequency of PDD. Subsequent long-term follow-up studies showed that 50–80% of PD patients will develop dementia, typically after 10–15 years of motor disability. Older age at PD onset, duration of motor symptoms, akinetic-rigid or postural instability gait disturbance phenotype (as opposed to the tremor-predominant subtype), reduced verbal fluency (naming the number of items belonging to a specific category, for example, animals, in 1 min), early hallucinations and mild cognitive impairment documented at first evaluation for PD increase the likelihood of PDD.[13]

Four salient issues related to the management of PDD are worth highlighting. First, from a diagnostic standpoint, clinical diagnostic criteria for PDD have been developed (Table 79.6).[19] Unlike AD, the initial impairment in PDD typically involves attention, executive function and visuospatial performance with only mild memory impairment in the initial stages. When evaluating cognitive function in PD, therefore, appropriate instruments that adequately evaluate the non-amnestic domains should be employed. In addition, tests that can be utilized by the clinician without the need for special expertise in neuropsychological testing have been proposed.[20] In the determination of dementia, it may also be difficult to judge the extent to which functional impairment is attributable to cognitive dysfunction rather than motor disability.

Second, the clinician should actively screen for and manage attendant neuropsychiatric and other non-motor issues that are common in PDD and can affect the quality of life of the patient and caregiver. The former include depression, anxiety, hallucinations, delusions and apathy. Among depressive mood disorders, dysphoria (40–58%) is more common than major depression (13%). Anxiety is common in PDD, especially in the 'off' period of treatment, and usually coexists with depression. The phenomenology of hallucinations is similar to DLB and comprises complex, formed visions of people or animals that are vivid in coloration. Delusions can be 'feeling of presence', phantom boarder, paranoid or grandiose type. Other non-motor complications in PDD include sleep disorders (such as restless leg syndrome, excessive daytime sleepiness and REM sleep disorders) and autonomic dysfunction.

Table 79.6 Diagnostic criteria for Parkinson's disease with dementia (PDD).

I Core features
1. Diagnosis of Parkinson's disease
2. Dementia syndrome developing within the context of established Parkinson's disease

II Associated clinical features

Cognitive features
- Impaired attention, executive function and visuospatial function
- Impaired retrieval failure-type memory (free recall that does not improve with cueing or in recognition tasks)

Behavioural features
- Apathy, depression, anxiety, delusions, hallucinations and excessive daytime sleepiness
- Presence of at least one behavioural symptom supports but is *not required* for the diagnosis of PDD

III Features that make the diagnosis uncertain but do not exclude PDD
1. Coexistence of another abnormality that may by itself cause cognitive impairment, e.g. presence of relevant vascular disease in imaging
2. Time interval between development of motor and cognitive symptoms not known

IV Features that are not compatible with diagnosis of PDD
1. Cognitive and behavioural symptoms appearing *solely* in the context of other exclusionary conditions, such as:
2. Drug intoxication
3. Acute delirium
4. Major depression
5. Probable vascular dementia by NINDS–AIREN criteria

Probable PD: criteria I–IV met
Possible PDD: criteria I and IV met, BUT II, III or both not met

Modified from Emre *et al.*[19]

Third, managing clinicians should be mindful of treatment-associated side effects that can occur with agents used for treatment of motor symptoms (such as levodopa, dopamine agonists and anticholinergic agents) and behavioural symptoms (such as antipsychotic agents). Severe neuroleptic sensitivity has been reported in up to 40% of exposed PDD patients. Among antipsychotic agents, clozapine and quetiapine have been reported to be better tolerated in PDD patients.

Fourth, there is evidence from randomized controlled trials of PDD patients that cholinesterase inhibitors can offer modest improvements in memory mirroring the degree seen in AD, and also attention and neuropsychiatric features (especially hallucinations). Tremors occurred more frequently with treatment, but the overall motor function did not decline. Although improved cognition has been reported in patients with mild Parkinson's disease

following the administration of levodopa, mixed results have been found in moderately to severely affected PD patients. A small randomized controlled study of PDD or DLB patients reported that memantine produced cognitive and global benefits but not in psychiatric symptoms; preliminary subgroup analyses suggested a more pronounce global response in PDD than in DLB.[18]

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a tauopathy characterized neuropathologically by marked midbrain atrophy, neurofibrillary tangles or neuropil threads in the basal ganglia and brainstem and tau-positive astrocytes. Clinically, it is the degenerative disorder most commonly confused with PD. According to the National Institute of Neurological Diseases and Stroke–Society for Progressive Supranuclear Palsy (NINDS–SPSP) criteria, key clinical features for probable PSP are onset at age 40 years or later, a gradually progressive course, paralysis of vertical gaze and prominent postural instability with falls in the first year of disease onset.[21] Other pertinent features include dysphagia, dysarthria leading to unintelligible speech and a dysexecutive pattern of cognitive impairment. Unlike PD, which is associated with delusions, hallucinations and depression, PSP tends to exhibit more apathy, anxiety, obsessive–compulsive behaviour and disinhibition.

Two main clinical subtypes have been described: (1) Richardson's syndrome (54%), which features early appearance of falls, absence of tremor, symmetry of signs and poor response to levodopa; and (2) PSP-parkinsonism (32%), characterized by delayed onset of falls, presence of tremor, asymmetry and response to levodopa. The presenting symptoms of PSP are often non-specific and include falls (62%), personality change (22%), giddiness and gait disturbance. In the first 2 years of disease, characteristic signs of vertical gaze paresis, dysarthria and dysphagia are subtle or absent. About 40% of PSP cases do not exhibit falls in the first 2 years, especially in the PSP-parkinsonism subtype. It is therefore not surprising that the diagnosis of PSP is often delayed with a mean time of 3.9 years from symptom onset to a correct diagnosis.[22]

Several features may alert the astute clinician to the possibility of PSP. These include early instability and falls, especially in the first year of symptom onset, speech and swallowing difficulties early in the disease course, florid frontal lobe symptomatology such as apathy, impaired abstract thought, decreased verbal fluency or frontal release signs, and a predominantly axial pattern of parkinsonism that shows an absent, poor or waning response to levodopa. The hallmark of PSP is vertical supranuclear gaze palsy, which is characterized by disproportionate limitation of downward gaze (in contrast to the limitation of upward gaze that occurs in normal aging and PD) occurring in the presence of intact oculocephalic reflexes. Among the earliest signs of PSP is slowing of voluntary downward saccades, which appears long before the restriction in amplitude of vertical gaze range.[22] This is easily tested by asking the patient to shift gaze quickly from the primary position to the floor. MRI may show disproportionate atrophy of the dorsal midbrain ('hummingbird sign') or increased iron deposition in the lateral putamen ('eye of the tiger' sign). PET/SPECT imaging shows hypoactivity of the frontal lobes.

Treatment is supportive and centred on falls prevention, and also aggressive surveillance and management of dysphagia. Cholinesterase inhibitors have not been shown to be useful in PSP. Unfortunately, the prognosis in PSP is generally poor, with progression to a chairbound state in a median of 5 years after symptom onset. Death, occurring at a median of 7 years, is often due to the sequelae from falls or dysphagia.

Corticobasal degeneration

Corticobasal degeneration (CBD) is a tauopathy which has substantial overlap with FTD and PSP. The cardinal neuropathological features are asymmetric cortical degeneration involving primarily the frontal and parietal regions, severe neuronal loss in the substantia nigra, ballooned achromatic cells and also tau-positive astrocytic plaques, neurofibrillary tangles and neuropil threads in the cortex, subcortex and brainstem. Clinically, CBD presents in the sixth or seventh decade of life with the following classical features: (1) unilateral parkinsonism that is unresponsive to levodopa; (2) asymmetrical movement disorder such as rigidity, dystonia or focal myoclonus; (3) cortical features such as asymmetric apraxia, cortical sensory loss (for instance, impaired two-point discrimination, agraphesthaesia and astereognosis), visual or sensory hemineglect and alien limb phenomenon; and (4) late-onset cognitive impairment.[22] In addition, CBD can also mimic other clinical syndromes such as primary progressive aphasia, frontotemporal dementia, progressive orofacial apraxia and or posterior cortical atrophy. Given the heterogeneous clinical presentation of CBD, it is unsurprising that the sensitivity of diagnosis of CBD is disappointingly low (30%) and patients with CBD pathology are often misdiagnosed with other conditions, most commonly FTD and PSP. Conversely, the pathological heterogeneity of the corticobasal syndrome means that those receiving a clinical diagnosis of CBD commonly demonstrate alternative pathologies at autopsy such as AD, Pick's disease, PSP and prion disease.

The myoclonus of CBD is typically focal, confined to the limb (usually the arm) and most prominent during voluntary action. Apraxia is classically of the ideomotor type, referring to inability to perform movements on command

that is not explained by motor or sensory abnormalities. The apraxia is most severe in the limb affected by dystonia or myoclonus and, rarely, can involve buccofacial structures. In the alien limb phenomenon, the affected limb performs actions that are not consciously intended by the patient. CBD has a unique cognitive profile of combined cortical and frontal-subcortical deficits that is marked by executive dysfunction, visuospatial disturbances, retrieval memory deficit and aphasia. Behaviourally, depression and apathy are frequent and often prominent. MRI may reveal asymmetric frontoparietal atrophy, while functional PET/SPECT neuroimaging shows asymmetric changes typically maximal in the frontoparietal cortex that are most severe on the side contralateral to the affected limb.

Treatment is largely supportive in nature. There is typically little or no levodopa response and disease duration is 7 years on average. Benzodiazepines, most notably clonazepam, may improve myoclonus. Botulinum toxin may be useful for the treatment of dystonia, eyelid movement disorders and drooling.

Multiple system atrophy

Multiple system atrophy is a synucleinopathy characterized by α-synuclein-positive glial cytoplasmic inclusions in glial cells with neurodegenerative changes in striatonigral or olivipontocerebellar structures. It is a sporadic, progressive, adult-onset disorder characterized by autonomic dysfunction that includes MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C).[23] Onset after age 75 years, hallucinations not induced by drugs and dementia make the diagnosis of MSA unlikely. Nonetheless, cognitive changes, particularly with executive function, have been reported in neuropsychological studies. Among subtypes, MSA-P tends to have more severe and more widespread cognitive dysfunction than MSA-C. MRI may demonstrate atrophy in the putamen, pontine and middle cerebellar peduncle and the hot cross bun sign on T2 images; marked cortical atrophy is unusual in MSA. SPECT/PET functional imaging shows striatal or brainstem hypometabolism. Progression is more rapid than idiopathic PD, with 40% of patients markedly disabled or wheelchair-bound within 5 years of onset. Treatment is mainly supportive. Fludrocortisone or midodrine may be used for treating symptomatic postural hypotension

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) denotes a spectrum of neurodegenerative disorders that are characterized by a progressive dementia syndrome with prominent behavioural and/or language dysfunction early in the course of the disease arising from relatively circumscribed frontal and temporal atrophy. Clinically, the relatively younger age of onset, the typical presentation of syndromes and focal asymmetric frontotemporal atrophy hint at the diagnosis of FTLD. FTLD is superior to 'dementia' as a generic term for this group of disorders, since patients may have progressive neurological dysfunction for substantial periods of time before meeting criteria for a dementia syndrome.

FTLD is a neuropathologically, genetically and clinically heterogeneous group of disorders. Histopathologically, both familial and sporadic FTLD can be broadly divided into FTLD-tauopathy and FTLD-U/TDP-43 types on the basis of immunohistochemical analysis.[24] Historically, FTLD has been subdivided into either a tau-positive or tau-negative disorder on the premise of two pathologically distinct substrates: (1) tau-positive pathology with or without Pick's bodies and (2) dementia lacking distinctive histopathology (DLDH) in the absence of any defining inclusions. Recent advances in immunohistochemistry techniques have elucidated that in the majority of FTLD cases erstwhile subtyped as DLDH, ubiquitin-positive/tau-negative intra-neuronal inclusions are actually present; some of these cases have clinical or pathological evidence of motor neurone disease (FTLD-MND) whereas others do not (FTLD-U). The field moved further forward with the discovery of TAR DNA-binding protein 43 (TDP-43), which is the major pathogenic protein underlying sporadic and familial FTLD-U and FTLD-MND, and also in amyotrophic lateral sclerosis. More than 95% of FTLD cases are TDP-43 proteinopathies (50–60%) or tauopathies (35–45%), with DLDH and TDP-43 negative ubiquitinated inclusions comprising the remaining 5%.

A family history of dementia is present in about 40% of first-degree relatives. About 10% of the familial cases and 0–3% of sporadic cases have been linked to specific mutations. Many of these mutations occur in the microtubule-associated protein tau (*MAPT*) gene on chromosome 17 and have been collectively referred to as FTD with parkinsonism linked to chromosome 17 (FTDP-17) in familial cases with evidence of parkinsonism. Mutations that have been linked to TDP-43 proteinopathies include the progranulin (PRGN) gene on chromosome 17 and the valosin-containing (VCP) gene, which cause the rare autosomal dominant disorder of inclusion body myopathy associated with Paget's disease of bone and FTD (IBMPFD).

It is estimated that 3–20% of all cases of dementia may be FTLD. FTLD is the second most common form of dementia in those who are younger than 65 years (after AD) and widely regarded as the third most common cause of neurodegenerative dementia overall (after AD and LBD).[25] Onset occurs most commonly between ages 45 and 65 years, although FTLD can present before the age of 30 years and also in the elderly. An epidemiological study in the USA reported FTLD incidence rates of 2.2 in the 40–49 age class, 3.3 in the 50–59 age class and 8.9 in the 60–69 age class. There

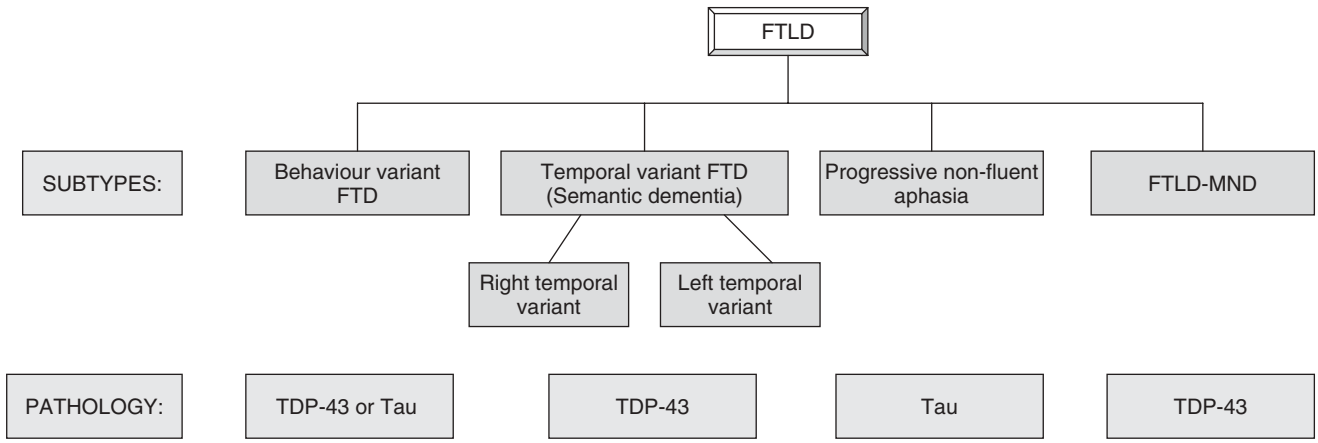

Figure 79.4 Clinicopathological correlation of the clinical subtypes of frontotemporal lobar degeneration (FTLD).

is an equal gender distribution. The duration of disease is in about 9 years in the FTLD-U and tau-positive groups, but significantly shorter at less than 3 years in FTLD-MND. Studies of age and education-adjusted autopsy-confirmed cases suggest that FTLD is associated with shorter survival and faster rates of cognitive and functional decline than AD.

There are three distinct clinical syndromes in FTLD, depending on the pre-eminent symptoms and the pattern of brain atrophy (Figure 79.4).[26] The commonest (at least 70%) is frontotemporal dementia (FTD), followed by semantic dementia (SD) (about 15%) and progressive non-fluent aphasia (PNFA) (about 10%). The right temporal variant of FTLD is a rare subtype characterized by asymmetric focal right temporal atrophy and can be considered to be the right hemispheric variant of SD. There can be substantial overlap between the three syndromes, and also with other clinical disorders, notably CBD and PSP. Motor neurone disease has been seen in combination with all three subtypes, but is most common with FTD and PNFA. All eventually worsen and produce a dementia syndrome. The clinical syndrome does not predict histological type, so that clinical distinctiveness itself does not imply aetiological difference.

Although there is too much overlap for reliable clinicopathological correlation, the clinical presentation may suggest which pathology is more likely (Figure 79.4).[27] Most patients with SD and FTLD-MND have TDP-43 proteinopathies, whereas PNFA (and CBD/PSP) is nearly always FTLD-tauopathy. The pathological correlate for bvFTD is evenly split between FTLD-tauopathy and FTLD-U/TDP-43. This concept of a TDP-43–tau pathological dichotomy has also been invoked in developing strategies for disease-modifying therapy that targets the underlying pathology in FTLD.

Frontotemporal dementia

Frontally predominant FTD, also known as behaviour variant FTD (bvFTD), is associated with atrophy of the frontal and/or anterior temporal cortex and subsequent involvement of the basal ganglia. Clinically, the salient characteristic is an early and profound alteration in personality and social conduct, occurring in the context of relative preservation of memory, spatial skills and praxis. Typical behaviours include disinhibition, apathy, social withdrawal, loss of empathy, hyperorality and dietary changes, diminished insight, neglect of personal hygiene, mental rigidity, perseveration, stereotypic behaviour and repetitive motor behaviours. Although repetitive and compulsive behaviours (such as tapping each wall twice upon entering a room, rereading the same book, walking to the same location repeatedly and clock-watching) can be present, bvFTD patients do not typically experience the feelings of anxiety and release from anxiety characteristic of obsessive–compulsive disorder. Dietary changes typically take the form of overeating, food fads and a preference for sweet foods. Utilization behaviours are common in the later stages; they refer to stimulus-bound behaviour in which patients grasp and use an object in their visual field despite its contextual inappropriateness (e.g. drinking from an empty cup). Also common are verbal stereotypies, involving the repeated use of a word, phrase or complete theme. When delusions occur, they are often bizarre and grandiose, but rarely persecutory. Progressive language loss or aphasia is often superimposed or appears simultaneously. Although there may be memory complaints, cognitive changes reflect frontal lobe dysfunction (inattention, poor abstraction, difficulty shifting mental set and perseverative tendencies) rather than a true amnestic syndrome. Table 79.7 summarizes the distinguishing features from AD.

Table 79.7 Distinguishing features between frontotemporal dementia and Alzheimer disease.

Clinical feature	Frontotemporal dementia	Alzheimer's disease
Cognitive		
Amnesia	Delayed until later in the course	Occurs early, *sine qua non* feature
Executive dysfunction	Early, progressive	Less prominent in early stages
Language	Reduction of speech output	Anomia with fluent aphasia; speech output preserved
Visuospatial skills	Relatively preserved	Involved early
Calculation	Relatively preserved	Involved early
Behavioural		
Disinhibition	Common	Occurs, but is less severe
Euphoria	Common	Rare
Stereotyped behaviour	Common and marked	Less common
Apathy	Common and severe with marked emotional blunting	Common, less severe
Dietary changes	Hyperorality and food fads (carbohydrate craving) common	Anorexia more common then overeating
Self-neglect	Common	Rare until late
Psychosis	Occurs, but is less common	Delusions and hallucinations more common
Imaging		
Structural MRI	Focal atrophy in frontal and/or anterior temporal lobes	Medial temporal lobe atrophy
	Usually asymmetric	Symmetrical
Functional. e.g. FDG-PET	Frontal and/or anterior temporal hypometabolism	Parietal and temporal hypometabolism

On physical examination, primitive reflexes such as grasping, pouting and sucking reflexes, occur earlier in the course then AD. Parkinsonian signs of akinesia, rigidity and tremor develop with disease progression. A minority of bvFTD patients develop fasiculations, wasting and weakness typical of motor neurone disease. Structural imaging with MRI is more sensitive than computed tomography (CT) in showing atrophy of the frontal and/or anterior temporal lobes, which is often asymmetric. Functional imaging such as PET or SPECT has high negative predictive value and a positive scan has high specificity for 'ruling in' FTD even in the absence of discernible atrophy on structural imaging. A longitudinal study of [^{18}F]fluorodeoxyglucose (FDG) PET imaging found that anterior hypometabolism progresses to include parietal and temporal regions over time, which may be mistaken for the parietal and temporal hypometabolism seen in AD. Functional imaging should therefore be performed early in the course of suspected FTD, when it is more likely to assist in differentiating FTD from AD.[25]

Semantic dementia

SD, also known as temporal variant FTD (tvFTD), begins with atrophy of the anterior temporal lobes with later involvement of the orbitofrontal cortex and basal ganglia. Clinically, patients with more significant *left* temporal atrophy present with progressive loss of ability to understand the meaning of words, although fluency is retained. Because of the loss of semantic knowledge, patients typically question the meaning of words they hear in conversation (for instance, 'What is spaghetti?'), giving the impression of impaired comprehension and repetition. Semantic paraphasic errors are common with word substitutions (such as 'food' for 'carrots') and later, fluent semantic jargon, often totally irrelevant to the questions asked or the topics discussed. They have difficulty reading irregular words due to the inability to move from orthograph to meaning (for example, 'gnat' is read as 'gunat'), although articulation, syntax and phonology remain intact. An unusual number of SD patients have an emergence of artistic talent in their dementia syndrome, reflecting the integrity and, possibly, disinhibition of right hemispheric activity. Clinical presentation in the *right* temporal variant includes prosopagnosia (impaired recognition of identity of familiar faces), topographic disorientation in familiar places, associative agnosia (impaired recognition of object identity) and, less commonly, complex visual hallucination. Typical behavioural changes in SD include irritability, impulsivity, bizarre alterations in dressing, mental rigidity and goal-directed compulsive collecting. Additionally, SD patients develop behavioural features that overlap considerably

with bvFTD. The main differential diagnosis is AD, which can also manifest as a progressive fluent aphasic disorder. However, AD patients exhibit a greater degree of amnesia and concomitant visuospatial and calculation dysfunction. In addition, although both groups exhibit medial temporal lobe atrophy, there is asymmetric hippocampal atrophy and greater atrophy of the anterior temporal region in SD patients compared with AD.

Progressive non-fluent aphasia

PNFA is associated with atrophy of the left inferior frontal lobe, anterior insula and basal ganglia. The dominant feature is disorder of expressive language, presenting as progressively worsening non-fluent spontaneous speech with shortened phrase length, agrammatism (omission or incorrect use of grammatical terms including articles and prepositions), phonological paraphasia with sound-based errors and anomia. There is often accompanying stuttering, speech apraxia, impaired repetition with paraphasic intrusions, alexia and agraphia. In the early stages, comprehension is preserved for word meaning, but impaired for syntactic relationships. Often, executive function and working memory are impaired. Behaviourally, these patients may be impulsive, apathetic or depressed, but are generally appropriate and many have retained insight. Many patients with PNFA ultimately develop a clinical syndrome suggestive of either CBGD or PSP that is confirmed by neuropathology.

Treatment

As with other dementias, the management of FTLD is multifaceted. Caregiver education and support, and also optimization of non-pharmacological measures are paramount. Pharmacological treatment is currently aimed at symptomatic treatment with a focus on management of difficult behaviours and cognitive impairment. A host of disease-modifying strategies targeting the underlying pathology in FTLD are under investigation and tau-based therapies are already under way in the preclinical stage of investigation for FTLD.

Consistent with the selective vulnerability of serotonergic neurons in FTLD, a systematic review of selective serotonin reuptake inhibitors (SSRIs) and trazadone suggests that these medications offer modest benefits for improving the behavioural symptoms of bvFTD. The use of trazadone may be limited owing to its sedating side effects. Behaviours that may respond to SSRI treatment include impulsitivity, disinhibition, repetitive stereotyped behaviours and obsessive–compulsive behaviour. Whereas depression is rare in bvFTD, it is more common in SD and PNFA patients and amenable to SSRI treatment. In general, apathy is recalcitrant to pharmacotherapy and can be a welcome relief for caregivers in the severely behaviourally disturbed patient. In some cases, bupropion (which has additional dopaminergic agonist properties) can be considered in FTLD patients with apathy and parkinsonism.[27] Atypical antipsychotic agents may be considered to treat delusions, severe agitation and aggression, but should be used sparingly in patients with FTLD owing to enhanced sensitivity to extrapyramidal side effects, somnolence, weight gain and exacerbation of apathy.

Less success has been reported in treating the cognitive symptoms of bvFTD. Unlike AD, there is no demonstrable cholinergic deficit in FTLD. Studies using cholinesterase inhibitors (ChIs) have produced mixed results. Although some open-label studies have reported a possible benefit, experience from a number of FTD-specialty clinics suggests that ChIs frequently worsen behavioural symptoms in bvFTD patients. Three open-label studies of memantine in bvFTD have been reported, all suggesting that memantine is well tolerated although no clear evidence of efficacy could be identified. A recent open-label study of memantine treatment in the three subtypes of FTLD demonstrated only a transient benefit in behaviour in bvFTD, but there was no other benefit in cognition, behaviour or motor symptoms in bvFTD and the other two subtypes.[28]

Motor impairments, including atypical parkinsonism or weakness from motor neuron involvement, are commonly observed with more advanced disease. When parkinsonism occurs early in the course of the disease, a trial of dopamine agonist therapy should be considered. Generally, axial instability and dysphagia are recalcitrant to such treatment, but patients may experience more fluidity of movements. Patients with FTLD should be evaluated thoroughly for signs of motor neuron disease and, when appropriate, referred to a neuromuscular specialist. Patients with FTD-MND can be started on riluzole, which is generally well tolerated and has low drug–drug interactions with antidepressants and memantine.[27]

Depression

Depression is common among the elderly. The term *pseudodementia* was coined to reflect impairment in thinking and memory that frequently accompanies depression. The cognitive domains affected in depression include slowed mental processing and deficits in attention and executive function. Individuals with late-onset depression tend to exhibit more significant cognitive impairment.

Making a diagnosis of depression in a patient presenting with cognitive impairment can be difficult, since the patient may not complain of classical mood changes or have comorbid medical conditions that confound interpretation of 'physical' symptoms of sleep, appetite/weight, psychomotor change and energy disturbance. Although certain clinical features can be helpful in the differential

diagnosis of dementia and depression, none are diagnostic and frequent exceptions and overlaps exist. It is helpful to keep in mind three possible relationships that can exist between depression and dementia.

First, the two conditions often coexist. Epidemiological data indicate prevalence rates of 30–50% for depressive symptoms among AD patients, especially in the earlier stages of dementia where insight is often retained. Depression does not generally have a profound impact on cognitive performance in early-stage AD. Hence it is often the experience that while antidepressant treatment of concomitant depression in dementia can result in impressive improvement in mood and quality of life, the cognitive impairment remains relatively unchanged.

Second, there is a growing body of evidence that baseline depression is a risk factor for incident dementia and cognitive decline.[29] Therefore, dementia needs to be entertained as a differential diagnosis in cases of long-standing depression where there is lack of cognitive improvement, despite adequate treatment of the underlying affective disorder.

Third, owing to the considerable overlap in symptoms, some individuals with dementia may be erroneously diagnosed as having depression instead. Features of depression such as loss of interest, decreased energy, psychomotor changes and decreased concentration lose diagnostic specificity in the presence of dementia. Affective symptoms such as guilt, expressions of worthlessness and suicidal thoughts, if present, are more useful in distinguishing depression from dementia. It is also important to give appropriate consideration to the proxy informant's subjective reports of symptoms of depression in a demented patient, as the latter tends to minimize or under-report depressive symptoms, particularly when there is lack of insight into the underlying cognitive deficits.

Since depression in the elderly is not always easily diagnosed, particularly in the context of dementia, an empirical trial of antidepressant therapy in cases of diagnostic uncertainty is a reasonable strategy. A 6–8 week treatment trial of an appropriate antidepressant without significant anticholinergic properties, such as the SSRIs, is relatively safe and can sometimes provide considerable improvement.

Medications

Strictly, medications cause a state of cognitive impairment secondary to chronic confusion or delirium rather than an actual dementia. As with depression, cognitive impairment due to medications is often superimposed on other dementing disorders. Virtually any medication, including many over-the-counter drugs, has been implicated. The commonest culprits are drugs that affect the cholinergic, dopaminergic, serotonergic and noradrenergic systems and can be remembered by the mnemonic ACUTE CHANGE IN MS (mental status) (Table 79.1).[30] Medications are potentially reversible causes of cognitive impairment, hence a high index of suspicion is required, especially if there is a clear temporal relationship between the onset of symptoms and change in type or dosage of medications. Removing or reducing unnecessary medications may improve cognition, even in patients with underlying neurodegenerative diseases such as AD.

Dementia with parkinsonism

General approach

The principal causes of cognitive impairment with parkinsonism in the elderly are listed in Table 79.8. When confronted with this diagnostic conundrum, a systematic approach would be to (1) exclude easily identifiable secondary causes and then (2) determine if the clinical picture supports a diagnosis of Parkinson's plus syndrome as opposed to idiopathic PD. Useful discriminating features in favour of Parkinson's plus syndrome are symmetrical onset of parkinsonism, absence of resting tremors and the presence of concomitant atypical features (history of poor response to levodopa, predominantly axial involvement, early severe dementia, early marked autonomic disturbance, gaze palsies and upper motor

Table 79.8 Causes of parkinsonism with cognitive impairment in the elderly.

Parkinson's disease
- Idiopathic
- Familial

Parkinsonism in other neurodegenerative diseases

Dementia with Lewy bodies
- Progressive supranuclear palsy
- Frontotemporal dementia with parkinsonism
- Multiple system atrophy (MSA)
  - MSA with predominant parkinsonism (MSA-P)
  - MSA with predominant cerebellar ataxia (MSA-C)
- Corticobasal degeneration
- Hallervorden–Spatz disease

Vascular dementia with parkinsonism

Post-encephalitic parkinsonism
- Encephalitis lethargica
- Other encephalitides, e.g. syphilis

Secondary parkinsonism
- Pharmacological: antipsychotic agents, especially the high-potency conventional agents and other dopamine blocking drugs
- Toxins: carbon monoxide intoxication, cyanide poisoning, methanol, ethanol
- Post-anoxic parkinsonism
- Dementia pugilistica
- Normal-pressure hydrocephalus
- Space-occupying lesions: tumours, blood clot, abscess
- Metabolic (e.g. Wilson's disease)

neuron findings). In a clinicopathological study that examined patients who exhibited two out of the three classic signs of parkinsonism (tremors, rigidity and bradykinesia), the strongest additional bedside predictor for idiopathic PD is the combination of (1) asymmetric onset, (2) no atypical features and (3) no alternative diagnosis.

In the clinical history, it is important to ascertain the onset, duration and progression of the illness. A younger age of onset would alert the clinician to familial syndromes, hereditary illnesses (e.g. Wilson's disease) and certain neurodegenerative causes such as FTLD and MSA. Cognitive decline without significant progression over time is not, in general, likely to be secondary to neurodegenerative causes since once symptomatic, these tend to be progressive. Chronology of presenting symptoms, in particular the temporal relationship between the onset of parkinsonism and dementia, can yield useful information. For instance, dementia onset more than 12 months after the initial motor symptoms of parkinsonism favours the diagnosis of PDD rather than DLB. Marked fluctuations in cognition, attention and alertness are pathognomonic of DLB and PDD, although it is prudent to exclude delirium and its myriad causes if the duration is short. A history of frequent falls early in the course of disease suggests PSP, although this can also be seen in PD, DLB, MSA and NPH. Early dysphagia or dysarthria is characteristic of PSP. Compared with AD, the degree of memory impairment in the group of dementias with parkinsonism is comparatively milder by disease stage and there are usually more neuropsychiatric features at the time of presentation. FTD patients are more likely to manifest euphoria and disinhibition, whereas visual hallucinations, delusions and misidentifications are more common in DLB and PDD. A detailed family history and medication review cannot be overemphasized. Other relevant history includes occupational history (e.g. dementia pugilistica results from recurrent significant head trauma and classically occurs in boxers), ethanol ingestion and significant illnesses (e.g. strokes, encephalitis).

Pertinent pointers during physical examination include examination of the eyes (impairment of vertical gaze with intact oculocephalic reflex in PSP), cerebellar signs (MSA-C), pattern of extrapyramidal involvement (PSP is characterized by predominantly axial as opposed to appendicular rigidity), postural blood pressure (orthostatic hypotension from autonomic dysfunction is a feature of MSA, but can also occur in DLB and PD; it can also be secondary to drug treatment with levodopa and dopamine agonists), higher cortical function (asymmetric limb apraxia and cortical sensory loss in corticobasal degeneration) and gait (apraxic gait typically in NPH, but also seen in Binswanger's disease and SIVD). Structural neuroimaging with CT or MRI can yield useful information about the differential diagnosis: hydrocephalus, space-occupying lesions, evidence of cerebrovascular disease such as lacunar infarcts, white matter hyperintensities or cerebral microbleeds, midbrain atrophy which is typical of PSP, pontine and cerebellar atrophy and the hot cross bun sign evident in MSA. Hypointensity of the striatum on MRI is generally against the diagnosis of idiopathic PD.

Conclusion

Non-Alzheimer dementias constitute a significant proportion of dementia aetiologies in epidemiological studies. It is important to diagnose non-Alzheimer's dementias accurately, as they often carry different prognoses and entail different treatment considerations from AD. Atypical features that arouse a suspicion of non-Alzheimer's dementia are most salient early in the course of disease and include prominent executive dysfunction, marked speech disturbance, marked behavioural changes (such as disinhibition, euphoria, stereotyped behaviour, apathy and self-neglect), frequent falls, vivid visual hallucinations, focal neurological deficit, extrapyramidal signs, vertical gaze limitation and asymmetric apraxia/dystonia. The major degenerative subtypes are vascular dementia (VaD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD) and frontotemporal dementia (FTD). These conditions have distinct clinical features and can often be reliably distinguished clinically from AD through the use of standard criteria and ancillary structural and functional neuroimaging modalities. With data from recently completed studies, and also recent advances in histopathological and diagnostic techniques, there is now a broader evidence base that the clinician can draw upon to guide the evaluation and management of non-Alzheimer's dementia.

Key points

- Vascular dementia is the most common dementia other than Alzheimer's disease.
- Lewy body dementia is associated with abnormal behaviours.
- Frontotemporal dementia is associated with apathy.
- Atypical features of dementia should arouse the suspicion that it is not due to Alzheimer's disease.

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CHAPTER 80

Treatment of behavioural disorders

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Introduction

Behavioural disorders in elderly individuals are most commonly caused by a dementing process. Individuals who suffered from lifelong psychiatric diseases, such as schizophrenia, might continue to exhibit symptoms of these diseases even in old age, but management of these symptoms follows general psychiatric practice. Therefore, this chapter concentrates on behavioural disorders caused by a progressive degenerative dementia.

Problem behaviour is a serious aspect of progressive dementias and is the most common reason for institutionalization.[1] The most common progressive dementias are Alzheimer's disease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia. A behavioural disorder may also be caused by a delirium that is induced by an acute medical or surgical condition (e.g. infections, dehydration, metabolic disorder) or by adverse effects of medications (e.g. drugs that have anticholinergic effect such as diphenhydramine, thioridazine and benztropine, cardiac medications such as digoxin and antihypertensive agents and drugs used to treat peptic ulcers such as cimetidine). Individuals with dementia are more sensitive to development of delirium and occurrence of delirium in cognitively intact individuals is an indication that the individual is at high risk of developing dementia.

Delirium is characterized by an acute onset of mental status change, fluctuating course, decreased ability to focus, sustain and shift attention and either disorganized thinking or an altered level of consciousness that resolves if the precipitating causes are removed (see Chapter 71, Delirium). However, diagnosis of delirium is not easy because some of these diagnostic criteria are not unique to delirium. Acute onset of mental status change may be caused also by a vascular dementia and fluctuating course of cognitive impairment is an important clinical diagnostic feature of dementia with Lewy bodies. Delirium is also not always a transient cognitive impairment because cognitive impairment resolves within 3 months in only 20% of patients with diagnosis of delirium. The specific symptoms of reversible dysfunction include plucking at bedclothes, poor attention, incoherent speech, abnormal associations and slow, vague thoughts. Delirium superimposed on dementia ranges from 22 to 89% of hospitalized and community populations aged 65 years and older with dementia and has several adverse consequences including accelerated decline, need for institutionalization and increased mortality. Therefore, the possibility that delirium is responsible for the onset of new behavioural symptoms should always be considered.

The diagnostic criteria for Alzheimer's disease include multiple cognitive deficits manifested by both memory impairment and at least one other cognitive disturbance (aphasia, apraxia, agnosia or disturbance of executive functioning). These cognitive deficits have to be severe enough to cause significant impairment in social or occupational functioning and have to represent a significant decline from a previous level of functioning. The course of Alzheimer's disease is characterized by a gradual onset and continuing cognitive decline. The cognitive impairment cannot be due to other brain disease, to systemic disturbances that can cause dementia or to drug-induced effects. Clinical diagnosis of the Alzheimer's disease is tentative and needs to be supported by neuropathological examination of the brain after the patient dies. Hence the most definite clinical diagnosis of Alzheimer's disease is 'probable Alzheimer's disease', which is made when there are no other possible aetiological factors and 'Possible Alzheimer's disease' when other possible aetiological factors are also present.

There are several diagnostic sets of criteria for vascular dementia and they differ from each other (see Chapter 75, Vascular dementia). Vascular changes are often present together with Alzheimer changes during brain autopsy. Hence it is difficult to exclude the possibility that a patient has Alzheimer's disease even when several criteria for vascular dementia are met.

Dementia with Lewy bodies (also sometimes called *diffuse Lewy body disease*) is characterized by a fluctuating course of cognitive impairment that includes episodic confusion with

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lucid intervals similar to delirium (see Chapter 79, Other Dementias). The diagnosis of frontotemporal dementia is based on personality changes and the presence of atrophy of the frontal brain areas in neuroimaging studies [computed tomography (CT) or magnetic resonance imaging (MRI) scan].

Physical causes of behavioural symptoms

Before any behavioural symptoms are ascribed to underlying dementia, possible physical causes have to be eliminated. Behavioural symptoms may be induced by an acute illness or by an exacerbation of a chronic condition. These conditions include cardiovascular disease, brain tumours, sensory deprivation (see Chapter 85, Disorders of the eye; Chapter 86, Auditory system), metabolic disorders, chronic obstructive pulmonary disease and anaemia. Acute illness can be an infection, acute abdominal conditions or an injury. Unrecognized pain is a common cause of behavioural symptoms and treatment of behavioural symptoms with acetaminophen may decrease the inappropriate use of psychoactive medications (see Chapter 69, Control of chronic pain). The pain could result from faecal impaction, urinary retention or unrecognized fracture, but the most common cause of chronic pain in nursing home residents is arthritis, followed by old fractures, neuropathy and malignancy. Detection of pain is difficult in individuals with dementia who cannot describe the pain and its location. A comprehensive evaluation of pain in non-communicative individual relies on the observation of facial expression, vocalization and body movements and tension and may use one of recently developed scales.[2]

Conceptual framework of behavioural symptoms of dementia

Although progressive degenerative dementias differ in their early presentation, the behavioural disorders that they cause in later stages of dementia are very similar. Several conceptual frameworks were developed to classify and describe behavioural symptoms of dementia on the basis of nursing, psychological or psychiatric concepts. A model integrating all these approaches postulates a hierarchy of causes of behavioural symptoms (Figure 80.1). At the core of these symptoms is the dementing process itself, which may be modified by the underlying personality of the individual. Primary consequences of dementia are functional impairment, mood disorders and delusions/hallucinations. These primary consequences, alone or in combination, lead to secondary consequences, namely inability to initiate meaningful activities, dependence in activities of daily living (ADLs), spatial disorientation and anxiety. Primary and secondary consequences of dementia cause peripheral symptoms: agitation, apathy, insomnia, interference with other residents, rejection of care, food refusal and elopement.

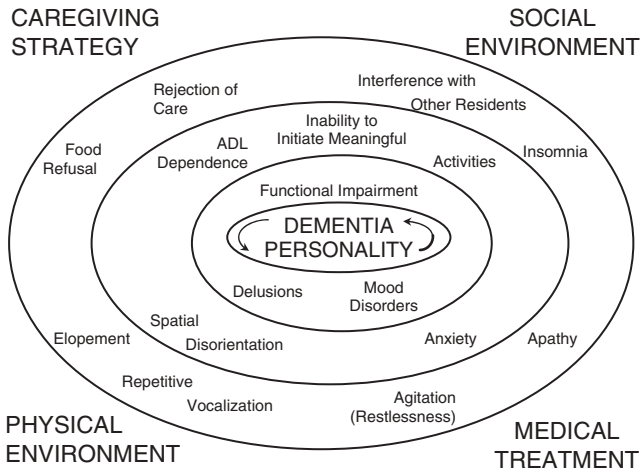

Figure 80.1 Comprehensive model of psychiatric symptoms of progressive degenerative dementias. Modified from Mahoney EK, Volicer L and Hurley AC. *Management of Challenging Behaviours in Dementia*, Health Professions Press, Baltimore, 2000, p. 2.

Peripheral symptoms may be caused by more than one of the primary and secondary consequences and each primary and secondary consequence can generate several peripheral symptoms. For instance, functional impairment may lead to an inability to initiate meaningful activities, dependence in ADLs and anxiety and agitation if stressful demands are made or agitation/apathy and repetitive vocalization if meaningful activities are not provided. Similarly, depression may lead to anxiety, worsening of the ability to initiate meaningful activities and to engage in ADLs, food refusal, agitation, insomnia and increased likelihood of rejection of care. Therefore, it is important to analyze the cause(s) of peripheral behavioural symptoms of dementia and treat effectively the primary or secondary consequences that are causing these symptoms instead of treating each peripheral symptom in isolation. Behavioural symptoms of dementia are influenced by four environmental factors: caregiving approaches, social environment, physical environment and medical interventions. The rest of this chapter describes in more detail elements of this model and therapeutic strategies that can be used.

Dementia and personality

Dementia is at the core of behavioural disorders. There is some evidence that premorbid personality traits are related to subsequent psychiatric symptoms. Patients who were more neurotic and less assertive before developing dementia are more likely to become depressed, whereas patients who were more hostile before developing dementia are more likely to have paranoid delusions. Patients who were neurotic and extroverted before developing dementia are more likely to engage in aggressive behaviour whereas previous agreeableness decreases

the probability of aggression. Unfortunately, there is no treatment currently available that would stop or reverse the course of progressive degenerative dementias. However, there are currently two classes of medications approved for the treatment of Alzheimer's disease (Table 80.1). There is some evidence that cholinesterase inhibitors may also be useful for treatment of vascular dementia and dementia with Lewy bodies. Although the primary effect of cholinesterase inhibitors is the improvement of cognitive function, their administration also leads to some improvement in behavioural symptoms of dementia. Meta-analysis of published reports regarding the efficacy of cholinesterase inhibitors showed that the behaviour of patients treated with cholinesterase inhibitors improved significantly and there was no difference in efficacy among cholinesterase inhibitors.[3] Memantine treatment was associated with a reduced severity or emergence of specific symptoms, particularly agitation and aggression.[4]

Cholinesterase inhibitors may not be effective enough to control all behavioural symptoms of dementia, but they may be useful as a first-line treatment. Caregivers of individuals with dementia treated with donepezil report lower levels of behavioural disturbances than caregivers of individuals not receiving this treatment. Donepezil patients were described as significantly less likely to be threatening, to destroy property and to talk loudly. Cholinesterase inhibitors are usually well tolerated, with diarrhoea and nausea being the most common adverse effects.

Functional impairment

The presence of functional impairment that interferes with daily activities is necessary for the diagnosis of dementia. Functional impairment is a result of several deficits affecting both cognitive and physical functions. Memory impairment causes inability to remember appointments and prevents the individual from participating in social games, for example, bridge. Speech impairment interferes with social contact and may result in an inability to understand spoken or written language. Apraxia leads to the inability to use tools and to continue engagement in previous hobbies. Spatial disorientation leads to the inability to take independent walks. Executive dysfunction leads to deficits in problem solving and judgement and prevents the individual from planning and executing an activity.

Functional impairment may cause three secondary consequences of dementia: dependence in ADLs, inability to initiate meaningful activities and anxiety if a person with dementia recognizes his/her limitations or if a caregiver has unrealistic expectations about the abilities of the care recipient. These secondary consequences may cause several peripheral symptoms: rejection of care, agitation, repetitive vocalization, apathy and insomnia. Functional impairment may involve both cognitive and physical components.

Treatment of the cognitive component of functional impairment involves both behavioural and pharmacological approaches. Because of the progressive nature of dementia, the deficits cannot be reversed. However, they can be minimized and the function maintained for as long as possible by creating an environment in which the individual with dementia can experience positive emotions and by preventing excess disability that may be induced either by expecting too much or by expecting too little from the individual (see Chapter 141, Occupational therapy: achieving quality in daily living). In the mild to moderate stage of dementia, memory aids may be helpful. Verbal instructions, presented automatically through simple technology, were helping persons with mild to moderate Alzheimer's disease recapture independence in morning bathroom routine, dressing and table-setting.[5] Practice may also help maintain cognitive skills. Patients who performed exercises that included word fluency, immediate and long-term verbal and non-verbal recall and recognition and problem solving improved their cognitive function and had fewer

Table 80.1 Drugs for treatment of dementia.

Generic name	Trade name	Mechanism of action[a]	Daily doses (mg)	Maintenance dose[f]
Donepezil	Aricept	Inhibition of AChE	5, 10[b], 23[c]	10 or 23 mg QD
Galantamine	Razadyne	Inhibition of AChE, nicotinic receptor modulation	8, 16, 24[d]	8–12 mg BID
	Razadyne ER			8–24 mg QAM with food
Rivastigmine	Exelon	Inhibition of AchE, inhibition of BChE	3, 6, 9, 12[e]	4.5–6 mg BID
	Exelon patch		4.6–9.5[d]	9.5 mg QAM
Memantine	Namenda	Modulation of NMDA receptors	5, 10, 15, 20[d]	10 mg BID
	Namenda XR		7, 14, 21, 28[d]	28 mg QD

[a] AChE, acetylcholinesterase; BChE, butyrylcholinesterase; NMDA, *N*-methyl-D-aspartate.
[b] The dose should be increased after 4–6 weeks.
[c] The dose should be increased after 3 months of treatment with 10 mg dose.
[d] The dose should be increased if a lower dose is tolerated for 4 weeks.
[e] The dose should be increased every week.
[f] QD, once per day; BID, twice per day; TID, three times per day; QAM, every morning.

behavioural problems whereas the control group continued to decline. These results indicate that procedural learning can occur in individuals with dementia and that the rate of decline can be slowed by the prevention of excess disability. Individuals may also maintain ability to perform an activity (e.g. playing dominoes) even after they lose the ability to explain the rules.

Pharmacological management of cognitive component of functional impairment involves drugs used for treatment of dementia described above. There is good evidence that both cholinesterase inhibitors and memantine improve functional abilities temporarily or slow the rate of their loss. Multifactorial approaches to maintenance of cognitive function were also developed. In a study involving administration of *Ginkgo biloba*, vitamin C, vitamin E and low-fat diet and including meditation, mind-body exercises, physical exercises, stress reduction techniques and cognitive rehabilitation exercises, the experimental group improved in verbal fluency, controlled oral word association test and paired association.[6]

The physical component of functional impairment includes decreased ability to ambulate and eat. Individuals with dementia become unable to ambulate independently because they cannot recognize objects in their path and because neurological impairment leads to unsteady or narrow-based gait (see Chapter 91, Gait, balance and falls). Both of these consequences lead to an increased risk for falls. If the risk for falls is managed by restraints, the individuals deteriorate further because of deconditioning and forgetting how to walk. It is important to maintain ambulatory ability for as long as possible because walking represents meaningful activity and because inability to walk increases the risk of intercurrent infections and pressure ulcers. Ability to walk can be promoted by a regular walking programme and by assistive devices, such as a Merry Walker.

Mood disorders

Mood disorders that can occur in individuals with dementia include depressive disorders and bipolar disorder. Depressive disorders are major depression with or without psychosis, dysthymic disorder and minor depressive disorder (see Chapter 83, Depression in later life: aetiology, diagnosis and treatment). Depression is very common in community-dwelling individuals with dementia and should be considered even in individuals with advanced dementia. Depression can cause or aggravate the inability to initiate meaningful activity and dependence in ADLs and often has an anxiety component. These secondary consequences may lead to several peripheral symptoms, such as apathy, agitation, food refusal and repetitive vocalization. Depression may also increase the likelihood of rejection of care because depressed individuals ignore ADLs. Depression also increases the propensity for escalation of rejection of care into verbal or physical behaviours directed towards the caregivers because even cognitively intact depressed individuals are angry and do not tolerate others. Depression is one of the main risk factors for development of verbally and physically abusive behaviour.[7] Depressive symptomatology may be improved by providing sufficient meaningful activities, but often requires treatment with antidepressants.

The first-line drugs to use for treatment of depression in individuals with dementia are selective serotonin reuptake inhibitors (SSRIs) (Table 80.2). These medications are usually well tolerated, with the most common adverse effect

Table 80.2 Selected antidepressants for treatment of depression in individuals with dementia.

Drug class[a]	Name (trade name)	Dose range (mg per day)	Frequency[b]	Elimination half-life (h)
Tricyclics	Desipramine (Norpramin)	25–100	TID	14–25
	Nortryptyline (Pamelor)	25–50	BID–QID	15–39
SSRIs	Citalopram (Celexa)	20–60	QAM/QHS	33–37
	Escitalopram (Lexapro)	10–20	QAM/QHS	27–32
	Fluoxetine (Prozac)	10–40	QAM	4–6 days
	Fluvoxamine (Luvox)	50–300	QHS	15
	Paroxetine (Paxil)	20–50	QHS	15–22
	Sertraline (Zoloft)	50–200	QAM	22–32
SNRIs	Venlafaxine (Effexor)	25–75	BID/TID	3–7
	Duloxetine (Cymbalta)	30–90	AD-BID	11–16
Others	Bupropion (Wellbutrin)	150–300	QHS	12–30
	Mirtazepine (Remeron)	15–45	TID, QHS	25–40
	Trazodone (Desyrel)	50–300	BID-TID	8

[a] SSRIs, selective serotonin reuptake inhibitors; SNRIs, selective serotonin/norepinephrine reuptake inhibitors.
[b] QD, once per day; BID, twice per day; TID, three times per day; QID, four times per day; QAM, every morning; QHS, every evening.

being diarrhoea. Since many individuals with dementia suffer from constipation, this usually is not a problem. SSRIs have some differences in their effects. Fluoxetine is the most stimulating of them and may result in increased agitation while paroxetine is sedating. Both fluoxetine and paroxetine and to a lesser extent sertraline affect cytochrome P450 isoenzymes and interfere with the metabolism of several drugs. Escitalopram may be an improvement over the first-generation SSRIs because it is faster acting than citalopram.

In individuals who do not tolerate SSRIs, venlafaxine or bupropion may be used. Another option is mirtazepine, which may promote food intake in individuals with decreased appetite. Tricyclic antidepressants are used infrequently because they cause significant adverse effects that are partly mediated by an anticholinergic activity. Because of this activity, they are contraindicated in individuals treated with cholinesterase inhibitors. Trazodone is a relatively weak antidepressant but is useful for treatment of insomnia, as will be discussed below. Electroshock therapy is effective in the treatment of depression in elderly individuals but may increase memory loss caused by dementia. Treatment of psychotic depression requires the addition of antipsychotics to the antidepressant therapy. However, addition of an antipsychotic may be also effective in the treatment of resistant depression without psychotic features.

The prevalence of manic episodes in individuals with Alzheimer's disease and other dementias is relatively low and most of the individuals who exhibit them have a history of mania before the onset of Alzheimer's disease. Manic episodes are more common in people with cerebrovascular disease, especially when it involves the right hemisphere and orbitofrontal cortex. Manic symptomatology can be a significant cause of agitation and may also lead to interference with other residents, for example, unwelcome sexual advances.

Manic symptomatology is best treated with mood stabilizers (Table 80.3). Lithium is a drug of choice for the treatment of bipolar disorder in young individuals, but its use in older individuals is questionable because the elderly may have age-related decreased kidney function or diseases and drug treatments that affect lithium excretion. Valproate may have effects as good as or better than those with lithium in acute mania and carbamazepine is also effective. However, gabapentin, lamotrigine and topiramate were not found to be effective in the treatment of acute mania. Anticonvulsants are sometimes used to treat behavioural symptoms of dementia even when there is no evidence that mania is present. Topiramate was recently shown to be as effective as risperidone in the treatment of behavioural symptoms of dementia.

Carbamazepine is effective in the treatment of agitation in nursing home residents with dementia, but it has significant adverse effects that include rash, sedation, ataxia, agranulocytosis, hepatic dysfunction and electrolyte disturbance. Valproate may not be effective and high doses are associated with unacceptable rates of adverse effects, mainly sedation. Other potential adverse effects of valproic acid include weight gain, hair loss, thrombocytopenia and hepatic dysfunction. Gabapentin was reported to be effective in the management of behavioural problems in individuals with dementia in case reports and case series, but there is no randomized control study. Lamotrigine is also sometimes used for the treatment of behavioural symptoms of dementia but there are only limited data about its effectiveness and its use risks the development of life-threatening rash.

Delusions and hallucinations

Delusion is a false belief, based on incorrect inference about an external reality that is firmly sustained despite evidence to the contrary. Delusions are often combined with hallucinations, which are sensory perceptions occurring without the appropriate stimulation of the corresponding sensory organ. Delusions occur in about half of individuals with Alzheimer's disease. Most of them have only delusions, some have both delusions and hallucinations, while

Table 80.3 Selected mood stabilizers used in dementia.

Name (trade name)	Dose range (mg)	Frequency[a]	Elimination half-life (h)	Therapeutic level
Lithium (Eskalith, Lithobid, etc.)	100–300	BID–QID	22	0.6–1.2 mequiv. l^{-1}
Valproic acid (Depakene); divalproex sodium (Depakote)	100–300	BID–QID	9–16	50–125 μg ml^{-1}
Carbamazepine (Tegretol)	100–200	BID	25–65 (12–17)[b]	4–12 μg ml^{-1}
Gabapentin (Neurontin)	300–900	TID[c]	5–7	Not measured
Topiramate (Topamax)	100–400	BID	19–23	Not measured
Lamotrigine (Lamictal)	25–100	QD	24–34	Not measured

[a]BID, twice per day; TID, three times per day; QID, four times per day.
[b]After chronic administration.
[c]After titration phase (during titration, 300 mg once or twice per day).

isolated hallucinations are rare. Isolated hallucinations are more common in dementia with Lewy bodies. Delusions and hallucinations could be caused by other conditions. The most common one is delirium, which was described above.

Delusions may be divided into two types: simple persecutory delusions and complex, bizarre or multiple delusions (see Chapter 81, Geriatric psychiatry). Simple persecutory delusions include delusions of theft or suspicion. Suspicions involve beliefs such as being watched or having an unfaithful spouse. Complex delusions may include a conviction about a family member or a pet being injured, about plots against individuals of certain religious faith and about wild parties happening on a non-existing floor of the nursing home. An example of complex delusion is Capgras syndrome, which consists of a false belief that significant people have been replaced by identical-appearing impostors. Complex delusions may also present as grandiose delusions often connected with euphoria and hypomanic mood.

The most common delusions in Alzheimer patients are paranoid delusions and the most common of those are delusions of theft, which occurred in 28% of patients. The cause of these delusions may be a memory problem of the patient, who forgets where he or she has put personal belongings. Delusions of suspicion were seen in 9% of the patients and more complex delusions in 3.6%. A common delusion of suspicion is that other patients in a long-term care facility are criticizing the patient behind his or her back. A stimulus for this delusion may be an innocent conversation in the hallway that is not heard very well by the patient and is misinterpreted. A very common delusion is the belief that the patient is much younger than his or her actual age. This delusion may be connected with misidentification, for example, of the patient's wife as his mother.

Onset of hallucinations in Alzheimer's disease is usually later in the disease progression, more than 5 years after the onset of dementia or more than 1 year after diagnosis. In approximately half of the patients the hallucinations are temporary, whereas in other patients hallucinations persist until death. Therefore, it is important to re-evaluate frequently the need for pharmacological treatment in demented individuals. Hallucinations and delusions are associated with greater functional impairment and are more common in individuals who have extrapyramidal signs, such as muscle rigidity, and in individuals who have myoclonus. Delusions and hallucinations may cause several secondary and peripheral behavioural symptoms of dementia. They may induce anxiety and spatial disorientation and they may also interfere with ADLs because the individual does not believe that the activity is needed. This results in rejection of care that may result in physical or verbal behavioural symptoms directed towards the caregivers.[7] Delusions and hallucinations may also lead to food refusal if the individual believes that the food is poisoned and to attempts to leave a home or facility if the individual believes that they have to go to work or go 'home'. Misidentification of other residents and staff may lead to interference with other residents or inappropriate behaviour towards the staff.

Treatment of delusions and hallucinations should consider their relationship to other behavioural symptoms of dementia. Some individuals with dementia have many delusions or hallucinations but are not bothered by them and they do not affect them behaviourally. In that case, no treatment is necessary. Otherwise, it is important to attempt non-pharmacological management of delusions and hallucinations before initiating treatment with antipsychotic medications. Non-pharmacological management should include attention to sensory perceptions, environmental modifications and behavioural strategies. Improvement of vision or hearing may decrease auditory delusions or visual hallucinations. Increased lighting, decreased noise, safe space for ambulation and social environment of a dementia special care unit will decrease the need to treat delusions and hallucinations, which cause behaviours that may be distressing to other cognitively intact residents. Behavioural strategies should recognize that reasoning cannot change behaviour because the individual with dementia does not understand reasoning and does not remember what he or she was told; therefore, caregivers have to change their behaviour. Caregivers should avoid the word 'no' and instead of arguing distract the individual from undesirable activity. It is better to accept the individual's reality than to try to orient them to our reality. Also, the person with dementia should always be made comfortable by smiling, by a positive tone of voice and by answering in a positive way even if the individual's speech does not make sense.

Pharmacological treatment of delusions and hallucinations utilizes administration of antipsychotics (Table 80.4). Older antipsychotics, represented by haloperidol, were potent antagonists of dopamine receptors. This led to a high incidence of extrapyramidal side effects and akathisia. These drugs are mostly replaced by newer (atypical) antipsychotics that have a more beneficial adverse effect profile. This improvement is due to their effect on other than dopamine receptors. The most significant is blockade of the serotonin 2A receptors that prevents extrapyramidal side effects and may also lead to improvement in apathy. This activity is present in risperidone and olanzapine. However, activity at other receptors may lead to some adverse effects. Olanzapine and quetiapine block histamine 1 receptors, resulting in sedation and weight gain. The weight gain is especially troublesome in olanzapine, because it could lead to the development of diabetes. Blockade of noradrenergic alpha-1 receptors, that is present in quetiapine and risperidone, may lead to orthostatic

Table 80.4 Selected antipsychotics used for treatment in dementia.

Name (trade name)	Dose range (mg)	Frequency[a]	Elimination half-life (h)	Most common adverse effects
Aripiprazole (Abilify)	10–15	QD	75 (94)[b]	Insomnia, somnolence
Haloperidol (Haldol)	0.5–1	QD–TID	18	EPS[c], tardive dyskinesia
Olanzapine (Zyprexa)	2.5–10	QD	30	Weight gain, anticholinergic, sedation
Quetiapine (Seroquel)	25–100	BID–TID	6	Sedation, hypotension
Risperidone (Risperdal)	0.25–1	QD–BID	3–20 (21–30)[b]	EPS, hypotension
Ziprasidone (Geodon)	20–40	BID	4–10	QTc prolongation, hypotension, rash

[a]QD, once per day; BID, twice per day; TID, three times per day.
[b]Active metabolite.
[c]EPS, extrapyramidal side effects.

hypotension. Aripiprazole has a novel mechanism of action because it is a partial agonist on dopamine receptors. This effect prevents excessive dopamine activity while preserving normal dopamine function.

Antipsychotics are frequently used not only for the treatment of delusions and hallucinations but also for behavioural symptoms that may not be related to them, despite several meta-analysis studies indicating a moderate effect of only a few antipsychotics, namely olanzepine, aripiprazole and risperidone.[8] A nationwide study found that 32% of antipsychotic drug users had no identified clinical indication for this therapy and that prevalence of antipsychotic use differed significantly in different facilities. This prevalent use of antipsychotics mostly continues, despite recent warning about their serious side effects. Antipsychotics increase the risk of stroke and sudden cardiac death,[9] increase threefold the incidence of serious events in community-dwelling individuals and twice the incidence in nursing home residents, and increase the incidence of hip fractures and overall mortality rate. Therefore, it is important to avoid the use of antipsychotics if possible and to use the lowest effective dose when they are being used. Alternative medications that may be used instead of antipsychotics are described below in the section on rejection of care.

Dependence in activities of daily living (ADLs)

ADLs are the activities that are needed for self-care and independent living. They include instrumental activities of daily living (IADLs) and physical activities of daily living (PADLs) sometimes called *basic ADLs*. Dependence in ADLs is the result of functional impairment induced by dementia, but depression or delusions may aggravate the dependence, resulting in excess disability. Therefore, it is important to determine carefully the reasons for dependence. If the individual is dependent in PADLs, physical care has to be provided. The individual with dementia might not recognize the reason for this care and might reject it. This rejection may escalate into combative behaviour, as will be described below. Thus, ADL dependence may lead to significant behavioural changes.

IADLs include shopping, preparing meals, travelling, doing housework and laundry, using the telephone, taking medications and managing money. Continued participation in ADLs is important for the self-esteem of the individual with dementia, but safety and stress induced by these activities have to be considered. IADLs should be simplified because the individual with dementia may still be able to participate in some steps but not in the entire activity (Table 80.5). Supportive services, such as a homemaker or meals-on-wheels, may allow an individual with dementia to continue living in their own home. Assistance may come in many forms: encouragement, verbal cues, visual cues (gestures) and physical guidance.

PADLs include bathing, dressing, grooming, toileting, walking and eating. PADL functional abilities decline in a predictable temporal order according to the complexity of the ADL – bathing, dressing, grooming, toileting, walking and eating. Bathing is an activity that most often results

Table 80.5 Examples of IADL adaptations for individuals with dementia.

IADL	Suggested adaptations
Shopping	Plan and go shopping with others Continue to help choosing purchases
Meal preparation	Prepare one dish, with steps presented one at a time
Using telephone	Help person list things to talk about before making a call Help person call relatives and friends Put pictures of people on preprogrammed telephone buttons
Money management	Simplify bill-paying routine Carry small amount of money Make small purchases with assistance on shopping trips

in rejection of care. Strategies for bathing dependence are described below. A significant improvement in dressing performance can be achieved by implementing strategies that allow the person to dress themselves independently with as little help as possible. Strategies for toileting difficulties include behavioural interventions (prompted voiding), establishing a routine, clothing modifications, making going to the bathroom easier, becoming familiar with and watching for cues indicating that the individual needs to use the bathroom, preserving dignity and physical assistance to reach a bathroom. Independent eating is promoted by encouraging independence while providing supervision and assistance, by creating a social mealtime environment and by simplifying the eating process. Walking ability can be maintained for as long as possible by the use of assistive devices, such as a Merry Walker.

Inability to initiate meaningful activities

This inability is caused by functional impairment involving loss of executive function due to damage of the prefrontal cortex, but may also be aggravated by depression. Lack of meaningful activities may result in apathy or agitation, repetitive vocalization and insomnia, if the individual with dementia sleeps during the day. Involvement in meaningful activities is important for maintenance of functional abilities, social involvement, feeling of success and accomplishment, improvement in mood and reduction of disruptive behaviour.

Management goals for people with the inability to initiate meaningful activity are prevention of excess disability, improvement of their interaction with the environment and their quality of life. Excess disability may be caused by impaired hearing or sight and by depression. Therefore, it is important to correct sensory impairment and treat depression even in individuals with advanced dementia. Individuals with dementia who are unable to initiate meaningful activities may be unoccupied and appear bored or not engaged with the environment, sitting motionless or wandering around aimlessly with increased risk for falls. They spend more time in a state of inner retreat and this withdrawn behaviour may manifest itself as lack of behaviour, somnolence, perseveration or non-directed agitation.

The goal of management of the inability to initiate meaningful activities is to create an environment with optimal stimulation and a steady flow of meaningful activities that are adapted to the functional capacity of the individual with dementia. There is a need for three different programmes to meet the needs of individuals with different severities of dementia. Individuals with mild cognitive impairment and mild dementia may be unable to participate in regular activity programming that is targeted to cognitively intact residents. They may benefit from a memory enhancement programme that provides separate activities promoting cognitive functioning and a social environment providing contact with similarly impaired non-judgemental residents.[10]

As the dementia progresses, it becomes increasingly difficult to keep the individual engaged during activities because of their short attention span. An activity programme that provides continuous programming throughout the majority of residents' waking hours is not only an effective way to reduce psychotropic medication, reduce falls and social isolation,[11] but also helps individuals with dementia to live with some purpose and meaning in spite of the disease. General guidelines for planning activities for individuals with dementia are listed in Table 80.6. In an institution, the programming should take into consideration the routine that the individual had before admission for long-term care. The continuous programming for moderate dementia should begin with a morning routine that may include the Pledge of Allegiance (in the USA), a patriotic song, newspaper or weather report discussion. Exercise programmes, food and beverages served in a social atmosphere, word games and spelling bees should follow. All these programmes should be 'no fail' opportunities to have fun. An individualized programme that was found to decrease agitation and improve mood is Simulated Presence Therapy.[12] At the end of the day, active participants are tired and ready for a video or a movie, a snack and a peaceful sleep.

As dementia progresses into the severe stage, it becomes even more challenging to engage individuals in meaningful activities. They tend to sleep during programmes

Table 80.6 Guidelines for planning activities for people with dementia.

Principle	Rationale
Focus on enjoyment, not achievement	The goals of therapeutic programme are to prevent excess disability and help the person 'feel good'
Create a 'failure-free' environment	Helps person maintain self-esteem
Design therapeutic activities to stimulate multiple senses	The ability to experience a range of human responses (emotions, behaviour) continues across mild, moderate and severe stages of dementia
Make activities part of daily routine	Maintain home-like routines Make all activities (including ADLs) meaningful Not an extra burden for the caregiver
Plan structured activities that employ previously learned motor patterns	These tasks require no new learning, yet can make the person feel useful and productive

and may have difficulty communicating. Another level of programming, one that has more individual attention and has less physical activities, helps meet their needs at this stage. This programming may be provided by nursing staff in a special room reserved for residents who do not benefit from other activities. Namaste Care is a programme that provides continuous activity without the need for additional staff.[13] The staff provide more touch, respect when the resident needs to take short 'naps' and use more visual cues. Other activities useful in that stage include pet therapy, massage and Snoezelen.[14] Meaningful activities should be provided even for individuals in the terminal stage of dementia because Alzheimer's disease rarely, if ever, progresses to the persistent vegetative state.[15]

Anxiety

Anxiety is defined as a vague, uneasy feeling, the source of which is often non-specific or unknown to the individual who is experiencing it. Anxiety is a feeling of distress, subjectively experienced as fear or worry and objectively expressed through autonomic and central nervous system responses. Anxiety can be a symptom of depression or be caused by disturbing delusions and hallucinations. It also can be caused by a primary anxiety disorder such as generalized anxiety disorder, phobia, post-traumatic stress disorder and obsessive–compulsive disorder. However, new-onset primary anxiety disorders are unusual in older adults. In most instances, older people with primary anxiety disorders have a history of them and it is therefore important to obtain complete personal and family psychiatric history.

Anxiety may also be a symptom of physical illness or be caused by medications. It may be induced by decreased delivery of oxygen to the brain caused by cardiac or pulmonary disease and by endocrine disorders such as hyperthyroidism and hypoglycaemia. Medications that may cause anxiety as an adverse effect include anticholinergic drugs, caffeine, steroids, decongestants, bronchodilators, alcohol, narcotics, sedative–hypnotics and other psychotropic medications. Anxiety also may be a withdrawal symptom in individuals dependent on alcohol, benzodiazepines or sedatives/hypnotics.

Anxiety is very common in Alzheimer's disease, occurring in 52% of patients in mid and late stages of the disease. The prevalence of anxiety increases with the progression of the disease,[16] but it is present together with suspiciousness even in individuals with mild cognitive impairment. Anxiety is even more common in individuals with vascular dementia and frontotemporal dementia than in individuals with Alzheimer's disease.[16]

Presence of anxiety is associated with reduced functional status in performing ADLs and with sleep disturbances. Over half of individuals with Alzheimer's disease who were experiencing anxiety woke up their caregivers at least once at night during the past week. The awakenings are associated with higher levels of patient anxiety and impairment in ADLs. Anxiety may also lead to agitation and repetitive vocalization.

Non-pharmacological management of anxiety is based on decreasing the stress level to which the individual with dementia is exposed. This may be accomplished by rest periods that prevent fatigue, positive communication strategies, prevention of overstimulation by providing a low-stimulation environment and avoiding unfamiliar situations. Pharmacological management should first consider treatment of the primary consequences of dementia that may cause anxiety: mood disorders and delusions/hallucinations. Only if this approach is not effective or there is strong evidence that the anxiety is caused by a primary anxiety disorder should anxiolytic medications be used. These medications include administration of benzodiazepines and buspirone (Table 80.7). Only short-acting benzodiazepines should be used and they may be useful also for short-term treatment of an anxiety-induced catastrophic reaction that usually causes extreme agitation.

Table 80.7 Selected medication for treatment of anxiety.

Drug class	Name (trade name)	Dose range and frequency[a]	Elimination half-life (h)	Side effects
Benzodiazepines	Alprazolam (Xanax)	0.25–0.5 mg TID	12	Sedation, impaired motor coordination, risk of falls, memory loss, respiratory depression, dependence, paradoxical reaction
	Lorazepam (Ativan)	0.5–1 mg BID or TID	15	
	Oxazepam (Serax)	10–20 mg TID or QID	8	
Azapirones	Buspirone (Buspar)	5–20 mg TID	Onset of action 3–6 weeks	Headache, nausea, drowsiness, lightheadedness
Antidepressants	See Table 80.2			
Antipsychotics	See Table 80.4			

[a]QD, once per day; BID, twice per day; TID, three times per day.

Trazodone is another medication that may be useful on an as-needed basis because of its antidepressant and sedative effects.

Spatial disorientation

Spatial disorientation is the misperception of immediate surroundings; not being aware of one's setting or not knowing where one is in relation to the environment. Spatial disorientation may cause misunderstanding of the environment and lead to development of fear, anxiety, suspicions, delusions and safety problems such as getting lost. Getting lost may also lead to the occurrence of interference with other residents if an individual with dementia invades their space and the inability to find a bathroom contributes to ADL deficit. In the early stages of dementia, the individual may become confused when they are in an unfamiliar place. In the later stages, the individual becomes confused even in previously familiar places.

Spatial disorientation may be related to damage of a specific brain area, the posterior cingulate gyrus, because hypofunction of this area measured by positron emission tomography (PET) was associated with disorientation for place. Another brain area that is necessary for place navigation and is damaged severely in Alzheimer's disease is the hippocampus. A healthy hippocampus uses two mechanisms for spatial orientation: cognitive mapping and cue navigation. Cognitive mapping requires cognitive processing to identify and store mental images of the most frequently encountered elements in a particular environment and the ability to make the connections among those elements. Cue navigation works by selection of a single landmark that directs an individual towards a specific location in the environment. Individuals retain these cues longer when they are familiar and are strongly associated with an environmental landmark. Another factor that participates in spatial disorientation in Alzheimer's disease is impaired depth perception. Because of this impairment, a change in colour of a carpet or tile may be perceived as a step or obstacle.

Management of spatial disorientation utilizes information from these studies by using pop-up cues and environmental landmarks. The pop-up cues strategy attempts to simplify the detection of the cue by providing one salient feature and colour contrasts. If the cue is complex, it requires more cognitive processing than a simple cue. Individuals with dementia, who have impaired attention span and cognitive processing, may not recognize complex cues. Colour contrast improves detection of the cue. Thus, a white toilet in a red bathroom is easier to find than a white toilet in a white bathroom. Environmental landmark strategy utilizes long-term memory by either keeping the environment unchanged or by using familiar objects as landmarks in a new environment. Personal or emotionally charged objects should be used as orientation devices. It is also important to simplify the environment by removing clutter and scatter rugs. Spatial orientation is promoted by signs on doors of common rooms, personal pictures or items by the door of individual rooms, adequate lighting that does not cast shadows that may be misinterpreted and by establishing a walking area with colour-contrasting borders.

Rejection of care

'Reject evaluation or care' is a new terminology used in the Minimum Data Set (MDS) 3.0 instead of 'resist care' used in MDS 2.0. Therefore, rejection of care will be used in this chapter instead of resistiveness to care, but both of these terms describe the same behaviour. These behaviours occur primarily during hands-on care that includes bathing, dressing, toileting, eating and administering medication. They can also occur when the caregiver attempts to redirect the individual with dementia.

Rejection of care is caused by either misperception of the need for care activity or by misperception of the caregiver's intent (see Chapter 59, Communication disorders and dysphagia). Thus, an individual who does not recognize that they have soiled clothing will reject a caregiver's attempt to change their clothes. Communication difficulties may prevent the individual with dementia from recognizing what the caregiver's intent is. In both cases, the individual with dementia does not cooperate with the caregiver and actively resists the caregiver's approach. If the caregiver insists on providing care, the individual with dementia may defend themselves from this unwanted attention, becomes combative and even strikes out. Such an individual may be labelled 'aggressive'. However, the patient perceives the caregiver as the aggressor and just defends themselves. Most individuals with dementia are not aggressive unless provoked and most 'aggressive' behaviours reported in the literature occur in the context of personal care.

Several factors increase the probability of rejection of care. Delusions and hallucinations may prevent recognition of the need for care or lead to misidentification of a staff person. Depression increases rejection of care because depressed individuals are angry and do not tolerate others.[7] Spatial disorientation may result in increased need for toileting because the individual cannot find a bathroom. Management of these factors may decrease rejection of care but the most important factor for its management is the caregiver approach. Therefore, caregiver behaviour should always be evaluated when rejection of care occurs before initiation of any pharmacological therapy.

The goal of care is to prevent the escalation of rejecting behaviour into combative behaviour. The approach used by the caregiver is crucial. Relaxed and smiling caregiver behaviour is related to calm and functional behaviour of the individual with dementia. It is important to avoid making

demands that create stress or are beyond the ability of the individual with dementia, avoid rushing through ADLs, avoid touching without warning, avoid painful procedures, avoid overstimulating the individual and express respect for the individual with dementia by allowing them to maintain some control. Distraction may be also used to direct the individual's attention away from the stressful stimulus. Engaging an individual in conversation on a favourite topic or reminiscing about happy memories that are retained takes the focus away from the task and places it on the person. This person-centred approach is effective even with individuals who have significant cognitive and language impairment. In an institutional setting, distraction may be accomplished by using two caregivers. While one caregiver engages the individual's attention by talking or singing, a second caregiver performs the ADL care.

Another important factor is the environment in which the care is provided. This is especially important for bathing. The bathroom should feel private and personal, it should be warm, have relaxing music, soft lighting, a low noise level, home-like furnishings, aromas to evoke memories and set mood and make the bathing experience pleasant, and the bathing equipment should be comfortable and functional. A very effective strategy for decreasing rejection of care is the modification of care procedures. Some individuals prefer to bathe in the morning and some in the afternoon or evening. It is also possible to make a shower more personal or to replace it with a bed bath that is much less stressful for an individual with dementia.

Pharmacological management should take into account the possible causes of rejection of care. A possibility that resistiveness is induced by pain that the individual experiences during care procedures should be considered and if pain is present premedication with analgesics before a care episode should be instituted. If symptoms of depression are present, antidepressant treatment often decreases the resistive behaviour. A double-blind randomized study indicated that citalopram is as effective as risperidone in the treatment of agitation and psychotic symptoms in patients with dementia. However, this effect requires effective antidepressant doses and duration of therapy as indicated by the DIADS study, where NPI score was improved only in those patients who obtained an antidepressant effect after treatment with sertraline.[17] Enhancement of antidepressant effect by addition of small doses of antipsychotics may be sometimes required.

There is also some evidence that inhibitors of cholinesterase have small beneficial effects on behavioural symptoms of dementia,[18] and one double-blind randomized study found that behavioural symptoms of dementia were improved by administration of prazosin.[19] Delusions are a common cause of resistive behaviour and, if the behaviour cannot be managed by behavioural strategies, antipsychotic therapy may be useful. In addition, treatment with mood stabilizers may also be effective since topiramide was recently shown to be as effective as risperidone in the treatment of behavioural symptoms of dementia.

Food refusal

One important goal of dementia care is to provide adequate nutrition by promoting eating and preventing food refusal. Food refusal may have several causes (see Chapter 16, The anorexia of ageing; Chapter 17, Weight loss; Chapter 59, Communication disorders and dysphagia). An individual with dementia may dislike institutional food, especially if they are of different ethnic background and were used to eating different food. Food refusal may also be caused by physical reasons, such as fatigue, overstimulation, constipation, medication-induced nausea, dehydration, toothache or ill-fitting dentures. Food refusal is an important symptom of depression and may also be caused by delusions about food being poisoned. In advanced dementia, when individuals develop swallowing difficulties, food refusal may be a consequence of choking on food and liquids. Finally, in the terminal stage of dementia, some individuals are unable to open the mouth and swallow.

Food refusal may lead to weight loss and malnutrition, although very often it is only occasional and the individual with dementia makes up for decreased food intake one day by eating more the next day. Management of food refusal should first consider personal and behavioural factors that may contribute to food refusal. It is important to obtain information about foods that the individual with dementia likes or dislikes, although sometimes food preferences change significantly as dementia progresses. Environmental factors that may cause food refusal are a chaotic or noisy dining area, inadequate staff time or staff knowledge of how to promote eating, unappealing food presentation and improper utensils. As dementia progresses, individuals become unable to use utensils and their failure to eat may not indicate food refusal. Serving finger food may allow them to eat independently for much longer.

If the behavioural and environmental interventions are ineffective, pharmacological management may be initiated. The most important is to eliminate depression and delusion as causes of food refusal by appropriate treatment with antidepressants or antipsychotics. If that approach is not appropriate or effective, food intake may be enhanced by administration of megestrol acetate or dronabinol. Megestrol acetate is a progesterone derivative with androgenic properties. It is used for the treatment of anorexia and cachexia in cancer and AIDS. Megestrol acetate improved appetite and wellbeing in nursing home patients.[20] Dronabinol is a cannabinoid derivative that is used for the treatment of anorexia in AIDS and the prevention of vomiting after chemotherapy for cancer. Dronabinol increased body

weight of institutionalized individuals with Alzheimer's disease[21] and may also improve their problem behaviours.

Tube feeding is not an appropriate strategy for the management of food refusal in individuals with advanced dementia. Tube feeding does not have any benefits for these individuals.[22] Tube feeding does not prevent malnutrition or infections and it does not increase survival in individuals with progressive degenerative dementia (see Chapter 48, Aspiration pneumonia). Nasogastric tubes may cause infections of the sinuses and middle ear and gastrostomy tubes may cause cellulitis, abscesses and even necrotizing fasciitis and myositis. Contaminated feeding solution may cause gastrointestinal symptoms and bacteriuria. Insertion of a tube may actually cause death from arrhythmia during insertion of a nasogastric tube and from perioperative mortality in percutaneous endoscopic gastrostomy tube placement. The occurrence of pressure ulcers is not decreased by tube feeding and it may actually be increased because of the use of restraints and increased production of urine and stool (see Chapter 133, Restraints and immobility). There is also no evidence that tube feeding promotes healing of pressure ulcers or improves the functional status of individuals with advanced dementia.

Insomnia

Sleep disturbances are common in elderly and probably even more common in individuals with dementia (see Chapter 54, Sleep apnoea and sleep disorders). A survey of individuals aged 65 years or older who were living at home showed that 28% had difficulty in falling asleep and 42% had difficulty both in falling asleep and staying asleep. Ageing affects sleep structure, resulting in less time spent in deep sleep and slightly more time spent in lighter stages of sleep. The elderly experience frequent night-time awakenings and fragmentation of sleep. They also sleep less efficiently, with their actual time asleep being only 70–80% of the total time spent in bed.[23]

Insomnia could be a primary condition but it may also be caused by other factors, including medical and psychiatric illness, medication use, specific sleep disorders, psychosocial factors and circadian rhythm changes. Insomnia is associated with respiratory symptoms, physical disabilities, use of non-prescription medications, depressive symptoms and poor self-perception of health.[23] Many medications that are used for the treatment of chronic conditions may affect sleep. These medications include decongestants, antiasthmatics, corticosteroids, antihypertensives, alcohol, caffeine, nicotine and thyroid preparations. Sleep disorders include sleep apnoea and periodic limb movement in sleep. Both of these conditions are very common in the elderly. Psychosocial factors include loneliness, bereavement and the lack of physical activity. Circadian rhythm changes differently in normal ageing and in Alzheimer's disease. In normal ageing, there is an advance of the sleep phase with early evening sleepiness and early morning awakenings. Even if elderly persons go to bed later, they may wake up early in the morning and be unable to go back to sleep.

In Alzheimer's disease, there is a delay in circadian rhythm resulting in an inability to go to sleep in the evening. This rhythm shift may be so pronounced that it results in complete reversal of day and night activities, with the individual with dementia sleeping during the day and staying up during the night. The delay in circadian rhythm may also participate in increased behavioural disturbances in the afternoon and evening that are often called *sundowning*. In contrast, individuals with frontotemporal dementia have no change in circadian rhythm of body temperature but an advanced rhythm of motor activity. Institutionalized individuals with dementia have extremely fragmented sleep, barely sleeping for a full hour and barely staying awake for a full hour throughout the day and night.

Management of insomnia should first utilize behavioural modifications. This includes avoiding caffeine, heavy meals and excessive amounts of alcohol before going to sleep, avoiding nocturia by decreased fluid intake in the evening, reviewing medications and limiting day naps to 30 min.[24] If behavioural modifications are not effective in reducing insomnia, the use of hypnotic medications may be considered (Table 80.8). Antihistamines should not be used because they have strong anticholinergic effects that can aggravate memory problems and can also cause other adverse effects. Most common agents used in the management of insomnia are benzodiazepines. Only short-acting benzodiazepines should be used to avoid daytime sedation and increased risk for falls. The shortest acting agent, zaleplon, is especially useful in individuals who have difficulty falling asleep. Trazodone is a non-tricyclic sedative antidepressant. Although there are few data to support the use of trazodone in non-depressed individuals, trazodone is useful in the treatment of insomnia associated with administration of stimulating antidepressants. Melatonin was not found to be an effective sleep agent in individuals with Alzheimer's disease.

Table 80.8 Drugs for treatment of insomnia.

Name (trade name)	Dose range (mg)	Elimination half-life (h)
Trazodone	50–300	4–9
Triazolam (Halcion)	0.125–0.25	2–3
Zaleplon (Sonata)	5–10	1
Zolpidem (Ambien)	5–10	1.5–3.5
Eszopiclone (Lunesta)	1–3	5.8

Apathy and agitation

Agitation is sometimes used as a term to label all behavioural symptoms of dementia. However, such a use of this term does not take into consideration the context in which a behaviour happens and does not differentiate between behavioural symptoms induced by caregiving activity (rejection of care) and symptoms that occur without provocation or environmental triggers. Therefore, it is more useful to limit the term 'agitation' to behaviours that communicate to others that the individual with dementia is experiencing an unpleasant state of excitement and that are observable without subjective interpretation, are not strictly behaviours that are invoked by caregiving activities, are unrelated to known physical needs of the patient that can be remedied and are without known motivational intent.[25]

Apathy is also a very common behavioural symptom of dementia and it is present in 27% of individuals with dementia living in the community and up to 92% of patients with advanced dementia. It is less common in individuals with dementia who lived with their spouses than in individuals who lived with others.[26] Unfortunately, apathy is very often not diagnosed and treated because apathetic patients do not cause a disturbance that would attract the attention of the caregivers. Apathetic individuals appear passive, demonstrate inattention to the external environment (e.g. fixed staring or immobility) and are uninterested in what is happening around them. Apathy and depression are not synonymous and there is no significant correlation between them. Apathy and depression also result in a different pattern of brain blood flow changes.

Both agitation and apathy denote a lack of psychological wellbeing. The most common cause of agitation and apathy is functional impairment, resulting in inability to initiate meaningful activities. If these activities are not provided, the individuals with dementia experience boredom and become apathetic. Alternatively, the individuals attempt to stimulate themselves and that may result in repetitive behaviours or repetitive vocalization. Therefore, the most important intervention for both apathy and agitation is the availability of meaningful activities. An enhanced continuous activity programme decreased agitation and social isolation significantly.[11] Because lack of meaningful activities may induce both apathy and agitation, both of these symptoms are often present in the same individuals. Treatment of agitation with sedating medications results in an even more apathetic individual.

However, agitation may persist even in the presence of these activities and may actually interfere with participation in activities. In that case, the agitation may be a symptom of depression or a consequence of anxiety that may be induced by delusions or hallucinations. Therefore, careful analysis of the likely causes of agitation and treatment of the underlying cause are necessary. Agitation may also be induced by changes in circadian rhythms. Delay in circadian rhythm is related to agitation in the afternoon and evening, sundowning. Resetting of the circadian rhythm by bright light exposure may improve sundowning, although the effect is not very strong.

Elopement and interference with others

Unsupervised wandering away from a home or institution may have severe consequences for the individual with dementia. Elopement exposes the individual to a risk of injury if they walk into traffic, to hypothermia in cold climates and hyperthermia with dehydration in warm climates. Wandering into rooms of other residents leads to conflict between residents, especially if the other resident is cognitively intact and resents the intrusion.

Wandering commonly describes the ambulating behaviour of a person with dementia when that person walks away from one area or walks into an area 'without permission'. Wandering may be caused by spatial disorientation or by delusions and hallucinations. An individual may be searching for something, attempting to fulfil unmet needs, escaping a threatening situation, reacting to reminders of departure near an exit or carrying out a predementia lifestyle function.

Longitudinal studies indicate that wandering behaviour starts on average 10 months after diagnosis of dementia in 40% of individuals but eventually occurs in 80% of all patients with dementia. Cross-sectional studies find prevalence of wandering between 15 and 28% with wandering characteristics similar in nursing homes and assisted-living facilities.[27]

Some individuals with dementia walk back and forth as if following a rhythm or pattern. In that case, their activity is called *pacing*. Pacing often occurs with speed and a sense of urgency and may seem to represent hyperactivity or restlessness. Pacing may pose a problem for the individual with dementia if it occupies so much walking time that the individual becomes overtired. Pacing may also interfere with sitting down to eat and may result in weight loss. Pacing actually consumes a considerable amount of energy and it was estimated that up to an additional 1600 calories are required to maintain adequate nutrition in individuals who pace. Another adverse effect of pacing may be foot problems, such as blisters.

Both wandering and pacing should not be a problem if they occur in a safe environment and may actually provide beneficial physical exercise. Interference with other residents may be avoided by providing care for individuals with dementia in a dementia special care unit, where residents may not mind the intrusion because they themselves have spatial orientation difficulties. Hence

the most important intervention for these behaviours is environmental modification. These modifications should provide a safe walking path away from exits and secure exits by disguising them or by a touch padlocking device. Wandering and pacing may also be a consequence of a lack of meaningful activities. Engaging an individual in activity might distract them from seeking an exit from a home or institution. Because an individual with dementia living in a community may wander away from a caregiver in public places and because the individual may elope from a home despite safety measures, it is important (in the USA) to register the individual with both the Alzheimer's Association Safe Return Program and the Medic Alert Program.

Environmental factors

Four environmental factors influence behavioural symptoms of dementia: caregiving approaches, social environment, physical environment and medical interventions. Each of them can be modified to prevent or improve behavioural symptoms. Caregiving approaches are most important for the rejection of care that may lead to verbal or physical behaviours directed towards the caregivers. The appropriate modification of caregiving approaches was described in the section Rejection of care.

Optimal social environment for care of individuals with dementia is a special care dementia unit (SCU). It eliminates problems related to interaction with cognitively intact nursing home residents who do not tolerate intrusion in their rooms and other people rummaging in their belongings. Research on the advantages of the SCU is not uniformly positive probably because of quality of care differences. When residents with dementia living on and off an SCU were compared, there was no difference in the use of physical restraints, but SCU residents were less likely to have had bed rails and to have been tube fed. SCU residents were more likely to be on toileting plans and less likely to use pads or briefs in the absence of a toileting plan. SCU residents were more likely to have received psychotropic medications, primarily antipsychotics.[28] Establishing an SCU increases occupancy rate and private pay census and decreases behavioural symptoms of dementia. The presence of an SCU also allows for the establishment of an activity programme specifically designed for individuals with moderate and severe dementia.[11]

The physical environment should prevent elopement and provide for safe ambulation and wandering. This environment is more easily created on an SCU. Using the Physical Environmental Assessment Protocol (PEAP), it was found that the SCUs were more supportive on six dimensions: maximizing awareness and orientation, maximizing safety and security, regulation of stimulation, quality of stimulation, opportunities for personal control and continuity of the self.[29] The environment should also help in the orientation of residents with dementia and provide stimulation by the presence of objects that may be handled safely by the residents.

Medical interventions may aggravate behavioural symptoms because demented individuals do not understand the need for these interventions and do not cooperate with diagnostic and therapeutic procedures. It is important to realize that even a routine intervention, such as measurement of blood pressure, causes some discomfort that may not be tolerated by individuals with dementia. Therefore, before any medical intervention is performed, its burden and benefits should be considered and compared with the goals of care for the individual patient. Some interventions may not be appropriate for a patient with advance dementia, for example, cardiopulmonary resuscitation.[30] Transfer to an acute care setting and use of antibiotics for treatment of generalized infections should be also considered carefully and not done as a default strategy. Tube feeding may not be indicated, as explained in the section on food refusal.

Key points

- Physical causes of problem behaviours need to be eliminated prior to attributing the causes to dementia.
- Demented persons may have concomitant depression or bipolar disorders.
- Caregiver behaviour may be responsible for rejection of care.
- The most important intervention for both apathy and agitation is the availability of meaningful activities.

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CHAPTER 81

Geriatric psychiatry

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Introduction

Care of older patients with mental health problems is immensely satisfying and rewarding. The most common mental health problems in older adults in the community include cognitive problems (e.g. dementia), depression and anxiety, alcohol and benzodiazepine misuse/abuse. In long-term care (LTC) settings, management of behavioural and psychological symptoms associated with dementia account for the majority of mental health problems. In acute care settings, delirium, depression and agitation in persons with dementia account for the majority of mental health problems in older adults. Abuse and neglect and severe mental illness (SMI), although less common in all settings, cause immense suffering and are associated with high health care utilization. Table 81.1 lists the most common mental health disorders in older adults. Thoughtful, individualized care of older adults with mental health problems takes time and can be facilitated by restructuring current practices (e.g. routine interdisciplinary assessment and management) and building new models of care (e.g. patient-centred medical home). Although old age may increase the likelihood of exposure to risk factors for the development of psychiatric disorders such as reduced social support, physical impairment and cognitive decline, it is important for primary care providers, patients and their families to realize that dementia and depression are not a normal part of ageing and that adequate treatment of these conditions can significantly enhance future health and wellbeing. Certain mental disorders are covered in greater detail in other chapters, although they are important disorders seen by geriatric psychiatry. These include depression, dementia and delirium.

Epidemiology

One in four older adults (aged 65 years and older) has at least one significant mental health problem/disorder.[1] The prevalence of mental health problems in the oldest old (aged 85 years and older) approaches 50%. The prevalence of mental health problems in the LTC population ranges from 65 to 100%. Older adults account for 14% of the population but almost 20% of all suicides. The prevalence of psychiatric disorders in older adults is expected to double over the next 30 years, making them a priority for healthcare and social care services.[2] The actual burden of mental disorders in older adults is probably underestimated because the stigma associated with mental disorders results in under-reporting of symptoms by older adults, under-diagnosis by healthcare providers (HCPs), clinical significance of sub-threshold symptoms and under-representation in epidemiological studies of high-risk older adults (e.g. medically ill, LTC residents).[3]

Challenges in geriatric psychiatry

There are a number of ways in which older adults uniquely express mental health disorders including under-reporting of symptoms, manifesting subclinical disorders and differential expression of symptoms based on age of onset. Clinically significant, subthreshold syndromes increase with age. Psychophysiological changes accompanying normal ageing, including alterations in sleep, appetite and psychomotor functioning, may make it difficult to diagnose clinically significant psychopathology. Cognitive impairment may further cloud the presentation of mood and psychotic symptoms. Late-life mental disorders often vary in their expression (e.g. less endorsement of affective symptoms in mood disorders) and treatment responsiveness (e.g. reduced response to antidepressants). In addition, the co-occurrence of general medical disorders with older age makes attributing functional limitations to mental health diagnoses more difficult. Common mental health problems (e.g. depression) often present atypically (e.g. with memory loss) in older individuals and loss of physical abilities, financial resources and family and friends can challenge even the most resilient amongst older persons. Many mental health problems (e.g. complicated grief) in older adults do not fit the conventional paradigm of disease. Older adults are

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Table 81.1 Common mental health disorders in older adults.

Depressive disorders
- Complicated grief
- Major depression
- Depression secondary to a physical health condition (e.g. stroke, Parkinson's disease, chronic pain)
- Dysthymic disorder

Anxiety disorders
- Generalized anxiety disorder
- Phobias (including fear of falls)
- Panic disorder
- Post-traumatic stress disorder

Cognitive disorders
- Delirium
- Alzheimer's disease
- Vascular cognitive impairment
- Dementia with Lewy bodies
- Parkinson's disease dementia
- Frontotemporal dementia
- Mixed dementia
- Mild cognitive impairment

Behavioural and psychological symptoms associated with dementias
- Apathy/indifference
- Depressive symptoms
- Psychotic symptoms
- Anxiety symptoms
- Sleep disorders (e.g. insomnia, excessive daytime sleepiness, REM sleep behaviour disorder)
- Agitation (e.g. wandering, hoarding)
- Aggressive behaviours (e.g. verbal aggression, physical aggression)
- Sexually inappropriate behaviours
- Eating disorders (e.g. anorexia, hyperphagia, pica)

Severe mental illness
- Schizophrenia
- Schizoaffective disorder
- Bipolar disorder

Other disorders
- Prescription-drug and substance abuse and dependence
- Drug-induced psychiatric disorders
- Personality disorders
- Adjustment disorders
- Delusional disorder

Table 81.2 Common standardized scales recommended in primary care.

Cognition (delirium)
- Confusion assessment method[4]

Cognition (dementia)
- Screening tools:
  - AD8[5]
  - Mini-Cog[6]
- Assessment tools:
  - Saint Louis University Mental Status (SLUMS) Examination[7]
  - MMSE[8]
  - MoCA[9]

Depression
- Screening tools:
  - Patient Health Questionnaire - 2 (PHQ-2)[10]
- Assessment tools:
  - Patient Health Questionnaire - 9 (PHQ-9)[11]
  - Geriatric Depression Scale 15-item and 30-item versions (GDS-15 and GDS-30)[12]
  - Cornell Scale for Depression in Dementia (CSDD)[13]

Harmful alcohol use and alcohol abuse
- Screening tools:
  - CAGE questionnaire[14]
- Assessment tools:
  - Short Michigan Alcohol Screening Test – Geriatric Version (SMAST-G)[15]

Agitation in patients with dementia
- Cohen-Mansfield Agitation Scale – Short Form[16]

Table 81.3 CAGE questionnaire.

C	Have you ever felt you ought to CUT DOWN on your drinking?
A	Have people ANNOYED you by criticizing your drinking?
G	Have you ever felt bad or GUILTY about your drinking?
E	Have you ever had a drink first thing in the morning (EYE OPENER) to steady your nerves or get rid of a hangover?

also more susceptible to the adverse effects of psychotropic drugs. Psychotherapy may need to be modified to accommodate cognitive and sensory deficits. All HCPs working with older adults should be prepared for these challenges.

The psychiatric interview of an older adult

The foundation of the diagnostic work-up of the older adult experiencing a psychiatric disorder is the diagnostic interview. Input from a reliable informant who is familiar with the patient is often crucial for accurate diagnosis. To supplement the clinical interview, the use of standardized rating scales is recommended. Table 81.2 gives a list of scales recommended for use in primary care, and Table 81.3 presents the CAGE questionnaire. All complaints, whether on the part of the patient or the family, must be taken seriously as they may signal treatable mental and physical health conditions. A simple screening question asking about the patient's mood and memory state is often informative. Coexisting sensory deficits (e.g. hearing, vision) and comorbid medical conditions (e.g. heart failure, chronic kidney disease, sleep apnoea, nutritional deficiencies) can all negatively affect mental health and their identification should therefore be part of any comprehensive assessment. The interview should routinely assess both risk and protective factors for late-life mental disorders. Involving

HCPs from other disciplines in comprehensive assessment is strongly recommended because the majority of older adults with mental health problems have multiple physical, interpersonal, social and financial problems that need to be addressed simultaneously.

Work-up

Laboratory testing, neuropsychological testing and neuroimaging can further assist in accurate diagnosis and identification of prognostic and protective factors in older adults with mental health problems. A comprehensive metabolic panel (CMP), thyroid-stimulating hormone (TSH) and vitamin levels (B_{12}, folate, D) to assess the aetiology of new-onset or resistant mental health problems are recommended. Certain clinical situations may dictate ordering urine tests (analysis, culture and sensitivity) and other laboratory tests (e.g. free testosterone levels in older adults with depression and other symptoms of testosterone deficiency). Before initiating antipsychotics, a baseline electrocardiogram (ECG) is recommended due to recent reports of sudden cardiac death associated with antipsychotic use. For residents in a hospice and for residents in the terminal stages of dementia, these baseline blood tests may not be ordered. Subtle seizure disorder should also be considered in the differential diagnosis of new-onset or atypical mental health syndromes and may require an electroencephalogram (EEG) and a referral to a neurologist. In some situations, a polysomnogram or nocturnal pulse oximetry may need to be ordered to rule out sleep disorders such as obstructive sleep apnoea. Neuropsychological testing is often crucial for accurate early diagnosis of dementing disorders [especially Alzheimer's disease (AD) and vascular cognitive impairment (VCI)] and differentiating it from depression and mild cognitive impairment (MCI). As part of comprehensive diagnostic work-up, neuroimaging such as computed tomography (CT) or magnetic resonance imaging (MRI) scans is recommended for all older adults with significant cognitive deficits, new onset mood or psychotic symptoms.

Interdisciplinary approach and individualized care plan

Most behavioural and psychological symptoms are best treated by an interdisciplinary team. Table 81.4 delineates the members who may constitute an ideal interdisciplinary team. Although the role of most of the team members listed in Table 81.4 is recognized by primary care providers, it is important to recognize the role of some key team members who are particularly important in LTC psychiatry. Recreational therapists use a whole host of tools and interventions (e.g. air mat therapy, sensory stimulation box) to address behavioural problems in LTC residents after a comprehensive assessment to identify background factors (e.g. cognitive ability) and proximal factors (e.g. psychosocial need states). Music therapists may lead group music activities as a part of a daily continuous activity schedule and also provide one-to-one music therapy for specific LTC residents who have depression and/or agitation. Art therapists use a variety of media, including paints, ceramics, natural materials and fabrics, to guide residents through everything from one-to-one painting sessions to group quilting projects.

Table 81.4 Members of an ideal interdisciplinary team.

Patient
Patient advocate, usually a family member/friend/caregiver
Geriatric psychiatrists/psychiatrists (Team Leader)
Nurse practitioners and physician assistants with geriatric mental health expertise
Primary care physician/geriatrician and physician extenders working with them
Pharmacists
Nurses
Certified nursing assistants
Social workers
Psychologists
Neuropsychologists
Registered dieticians
Chaplains and members of the clergy
Geriatric care manager
Physical therapist
Occupational therapist
Speech therapist
Music therapist
Recreational/activities therapist
Art therapist
Aromatherapist

The HCP should work with patient, their family members and other team members to develop and implement an individualized care plan for mental health problems and also for general medical and social problems. Determining which interventions are realistic and monitoring (and documenting) the response to the interventions are recommended. Trying to anticipate adverse events (such as constipation with pain medication) and planning interventions for the adverse event during care planning are also recommended.

Depression

Late-life depression is a heterogeneous group of disorders. Late-life depression is prevalent and eminently treatable. Late-onset depression may be a prodrome of late-life dementia and may also promote neuropathogenic processes that eventually cause dementia. Depression has been

associated with increased rates of cardiovascular illness and mortality after myocardial infarction. Depression and anxiety typically co-occur. Electroconvulsive therapy (ECT) remains the most effective treatment for depression in older adults. Antidepressants (especially for severe and or chronic depression) combined with psychotherapy is recommended for cognitively intact older adults with depression. Newer brain stimulation therapies (e.g. repetitive transcranial magnetic stimulation, vagal nerve stimulation, magnetic seizure therapy and deep brain stimulation) have not been well studied in older adults with depression and hence their use is not recommended except in academic/research settings.

Bereavement

Bereavement is associated with declines in health, increased utilization of healthcare resources and increased risk of death. Complicated bereavement may be distinct from major depression and formal criteria have been proposed. Complicated bereavement includes symptoms such as extreme levels of 'traumatic distress', numbness, feeling that part of oneself has died, assuming symptoms of the deceased, disbelief or bitterness, and symptoms endure for 6 months. Brief dynamic psychotherapy, traumatic grief therapy, crisis intervention and use of support groups can significantly reduce grief symptoms. Antidepressants may also be considered to treat complicated bereavement.

Severe mental illness

About 1% of the US population above the age of 55 years have severe mental illness (SMI). Mental health disorders considered as SMI include bipolar disorder, schizophrenia and schizoaffective disorder. Cognitive deficits, poor physical health and movement disorders are also experienced by a majority of older adults with SMI and they worsen adaptive functioning. Although suicide remains an important cause of mortality for this population, cardiovascular disease is the leading cause of death. Cardiovascular death among those with SMI is 2–3 times that of the general population. This is in part due to poor access to and use of quality healthcare services and high rates of obesity, diabetes and hyperlipidaemia (often exacerbated by antipsychotics). Older adults with SMI have difficulty complying with care regimens for chronic medical conditions such as diabetes and hypertension and have poor dietary habits. Older adults with SMI commonly face, in addition to persistent symptoms, increasing medical morbidity, limited financial resources and social impoverishment. Among homeless older adults, there is a high prevalence of SMI and cognitive impairment. Poor adherence to medication treatment for both mental and physical health conditions is common in older adults with SMI and has devastating consequences. Adherence problems are complex, determined by multiple factors and thus require a high index of suspicion and customized interventions that are focused on the underlying causes.

Bipolar affective disorder and late-onset mania

When an older adult presents with manic symptoms in later life and has no past history of bipolar disorder, a thorough work-up is recommended to identify general medical conditions that could cause manic symptoms (e.g. right hemisphere stroke, frontotemporal dementia) or drug-induced mania (e.g. corticosteroids or stimulants). Most older adults with bipolar disorder have had the disorder from their young adulthood, although onset as late as in the ninth and tenth decades has been reported. Late-onset bipolar disorder (onset after age 50 years) is commonly associated with comorbidities such as hypertension, diabetes or coronary artery disease and neurological disorders. There is high prevalence of cognitive dysfunction (especially executive dysfunction), frequent abnormalities on structural neuroimaging (e.g. cerebral white matter hyperintensities) and association with stroke. It is less likely to be associated with a family history of mood disorders. Older manic patients seldom display racing thoughts or euphoric/elated mood characteristic of younger adults and are more likely to be irritable, argumentative, angry, paranoid and disorganized. Mixed states are more common than in the younger population and psychotic symptoms are less common. Older adults often have more frequent episodes of mania and depression, with a shorter (e.g. rapid cycling) duration of symptoms than younger patients. Pharmacological interventions (e.g. atypical antipsychotics, valproate) combined with psychosocial interventions (e.g. psychotherapy, family and patient education) are needed for successful outcomes. ECT should not be considered only as a last treatment option, but should be considered in all older adults with bipolar disorder (including those with mild to moderate symptom severity), especially in those with a history of previous good response to ECT.

Schizophrenia

Schizophrenia is less prevalent than dementias and depression in older adults. However, the total health expenditures for older adults with schizophrenia exceed those of older adults with dementia and depression. Onset of illness is typically in early adulthood, with a small but distinct subgroup developing disease after the age of 45 years. Late-onset schizophrenia has a higher prevalence of the paranoid type, less severe negative symptoms, over-representation of women and requires lower doses of antipsychotic medications compared with early-onset schizophrenia. Most

of the older adults with schizophrenia have been active smokers for many years. Older adults with schizophrenia have a high prevalence of vascular risk factors (e.g. obesity, hypertension, diabetes, high cholesterol) and vascular disease (e.g. coronary artery disease). Therefore, treatment interventions should include efforts to control these risk factors optimally. Most older adults with schizophrenia live in the community, are stable, but remain symptomatic and functionally impaired. Sustained remissions, although uncommon, can occur even in older adults with chronic schizophrenia. Pharmacological interventions (primarily atypical antipsychotics) combined with interventions for psychosocial rehabilitation (such as social skills training, cognitive remediation, supported employment, residential alternatives) is often necessary for optimal outcomes. Assertive community treatment and case management greatly increase the success of these interventions.

Late-life psychosis

There is an increased incidence of psychotic symptoms (delusions and hallucinations) in older adults in contrast to younger adults. Older adults presenting with psychotic symptoms for the first time need a thorough evaluation to identify underlying causes such as dementia, delirium, depression, general medical conditions (e.g. cancer) or drug-induced psychoses. If the work-up is negative, a diagnosis of late-onset schizophrenia or delusional disorder may be entertained.

Cognitive disorders

These primarily include dementing disorders, delirium, cognitive impairment no dementia (CIND), mild cognitive impairment (MCI) and vascular cognitive impairment (VCI).

Dementing disorders

It is important to evaluate formally and diagnose specifically the type(s) of dementia. Comorbid physical and mental health conditions (e.g. nutritional deficiencies, depression) that may accelerate cognitive and functional decline should be looked for and promptly treated. There exists a minimal set of care principles for patients with AD and their caregivers that all clinicians are recommended to follow.[17] The goals of care are (1) to delay disease progression, (2) delay functional decline, (3) improve quality of life, (4) support dignity, (5) control symptoms and (6) provide comfort at all stages of dementia. Older adults with dementia-related symptoms of agitation and aggression should first be managed with psychosocial/environmental interventions. Pharmacological interventions (including antipsychotics) should be used only when psychosocial and environmental interventions have failed to control behavioural disruption adequately.[18] The findings related to antipsychotic drug safety (e.g. increased risk of mortality and stroke) should be taken seriously by clinicians in assessing the potential risks and benefits of treatment and in advising families about treatment. Better matching of the available psychosocial/environmental interventions to the patient's strengths and interests may not only reduce agitation but also prevent agitation and depression in persons with dementia.

Delirium

Although there are many potential causes of delirium, a 'final common pathway' involving a concomitant decrease in cholinergic tone and increase in dopaminergic tone in relevant brain regions has been hypothesized. Management of behavioural disturbances associated with delirium is primarily through psychosocial environmental interventions (e.g. improved sleep hygiene, range-of-motion exercises, ambulation, reorientation and cognitive stimulation).[19] Low doses of antipsychotics such as parenteral haloperidol may be needed for acute control of severe agitation.

Mild cognitive impairment (MCI) and cognitive impairment no dementia (CIND)

Many conditions may cause cognitive impairment, which may not meet current diagnostic criteria for dementia. Within this heterogeneous group CIND, there are disorders associated with an increased risk of progression to dementia. MCI represents several clinical subtypes, in which symptoms may relate directly to a transition to a more serious neurodegenerative disease. A substantial minority of MCI cases revert to 'normal' cognition over 1–2 years.

Vascular cognitive impairment (VCI)

Cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia (first being AD) and contributes to cognitive decline in the neurodegenerative dementias. The term vascular cognitive impairment (VCI), which is characterized by a specific cognitive profile involving preserved memory with impairments in attentional and executive functioning, has been proposed. Important non-cognitive features of VCI include depression and apathy.

Substance abuse

The need for substance abuse treatment among Americans over age 50 years is projected to double by 2020, according

to a report by the Substance Abuse and Mental Health Services Administration (SAMHSA). Alcohol abuse is the most common form of substance abuse in older adults. The 1 -year prevalence rate for alcohol abuse and dependence in the community is 2.75% for elderly men and 0.51% for elderly women. The prevalence rates are higher in primary care settings, where at-risk drinking has been estimated to be 5–15%. The prevalence of substance abuse may be underestimated because of the limited applicability of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition text revised (DSM-IV TR) criteria to the older adult population. Primary care physicians (PCPs) and emergency care providers can play a crucial role in early identification and initial management of addiction problems in older persons. Among older adults with chronic physical and mental health disorders, even modest alcohol consumption can lead to excessive disability and poorer perceived health. PCPs rarely ask about when and how much their older patients drink or what effect alcohol may have on their lives. In addition, older adults and their relatives are often in denial about the extent and effects of their drinking habits because the same amount of alcohol now causing difficulties had no untoward social or physical effects in middle age. PCPs are often not aware of recommended upper limits of healthy intake of alcohol and are in denial regarding the harmful effects of even 'social drinking' that typically exceeds recommended upper limits of alcohol intake. Older adults with alcohol abuse also face greater risk for suicide. Older adults with alcohol abuse are more likely to present with physical symptoms and to be admitted to medical or surgical units than younger patients with alcohol abuse. A non-judgemental and tactful approach is recommended in asking about and attempting to treat alcohol abuse, especially in ageing women. There is insufficient evidence to endorse pharmacological interventions (e.g. disulfiram, naltrexone, acamprosate) for alcohol abuse in older adults. Brief interventions (5 min for five brief sessions) targeting a specific health behaviour (at-risk drinking) by primary care providers are often fairly effective. Specific advice about the dangers of combining alcohol with prescription and over-the-counter (OTC) medications, especially psychoactive agents, should be given and regularly reinforced.

As 'baby boomers' age, illicit drug use among the over-50 population is also rising. Illicit drugs include marijuana, cocaine and the non-medical use of prescription drugs. An estimated 4.3 million adults aged 50 years or older used an illicit drug in the past year, according to SAMHSA. Age-related physiological and social changes make older adults more vulnerable to the harmful effect of illicit drug use. All older adults with illicit drug use (current or past) should be screened for hepatitis C and HIV infections.

Misuse and inappropriate use of prescription medications (especially benzodiazepines but also opiates) are a substantial issue in this population. The presence of a psychiatric disorder is a risk factor for prescription drug dependence in older adults. Benzodiazepine use increases with age and older adults tend to be on higher doses. Depression in older adults often presents with features of anxiety disorder and may be inappropriately treated with benzodiazepines rather than an antidepressant and/or psychotherapy. Signs of prescription drug abuse in older people include loss of motivation, memory loss, family or marital discord, new difficulty with activities of daily living, trouble with sleeping, drug-seeking behaviour and doctor shopping. Most misuse can be treated outside specialized substance abuse treatment programmes through education of patients, families and providers. Self-help groups (e.g. Narcotics Anonymous) is unlikely to benefit an older adult with prescription opioid abuse. In older adults, safe withdrawal may take weeks to months compared with days to weeks in younger adults. Implementation of non-drug interventions to treat chronic pain and insomnia play an important role in treatment of benzodiazepine and opiate misuse.

Anxiety disorders

Anxiety disorders are the most prevalent but under-treated psychiatric disorders in older adults. Common themes of anxiety in older adults include worries about physical illness and its impact on quality of life, including pain, disability and the possibility of death. These feelings can often be exacerbated by feelings of isolation and dependence in the LTC or hospital setting. Substantial comorbidity of medical and anxiety disorders with the possibility that physiological symptoms of anxiety can be a manifestation of a medical condition or adverse effects of a drug frequently confound and complicate proper detection of anxiety disorders in older adults.

Generalized anxiety disorder (GAD) is the most common anxiety disorder in older adults. Half of older adults with GAD have had symptoms for most of their lives, whereas the remaining half report developing GAD within the last 5 years. Many older patients with onset of panic attacks in early life continue experiencing symptoms in later life. New onset of panic attacks in older persons requires a thorough evaluation to detect underlying general medical condition(s) as its cause. Phobias are prevalent, chronic and persist into old age. Fear of falling is a typical phobia seen in older adults (especially those with history of fall and fracture) but is rare in younger adults. Post-traumatic stress disorder symptoms may recur later in life and recent losses or dementia may trigger a recurrence or emergence of symptoms for the first time in older adults at risk (e.g. war veterans/survivors, victims of abuse).

Incapacitating anxiety symptoms are common in patients with certain general medical disorders (e.g. chronic obstructive pulmonary disease, patients with

pacemakers, Parkinson's disease). Anxiety symptoms occasionally may be due to an underlying physical health condition (e.g. hyperthyroidism) or be drug induced (e.g. secondary to OTC sympathomimetics) or drug-withdrawal states (e.g. alcohol withdrawal).

Treatment of anxiety symptoms and disorders in older adults has typically involved the use of benzodiazepines, which are often effective but problematic because they are associated with a high risk of cognitive impairment, falls and fractures. Safer and equally effective (in the long term) alternatives to benzodiazepines include buspirone, antidepressants [e.g. selective serotonin reuptake inhibitors (SSRIs)], relaxation training and cognitive behaviour therapy. The therapeutic effects of antidepressants and buspirone may take up to 6 weeks to become noticeable. Judicious short-term use of short-acting benzodiazepines (e.g. lorazepam) may be necessary if symptoms are incapacitating until the other interventions become effective.

Geriatric psychiatry emergencies

Suicide

Some 20–50% of older adults who commit suicide have seen their PCPs within the week preceding their suicide. Older adults in general give fewer warnings, use deadlier methods (71% using firearms) and have lower attempts to completion ratios (4:1 versus 200:1 in adolescents), making it more difficult to identify older adults at risk of suicide. Clinicians are less apt to decide that suicidal thinking in an older adult is a serious condition which may respond to treatment. Depression is the strongest risk factor for suicide in older adults and for suicide's precursor, suicidal ideation. Other risk factors include, but are not limited to, alcohol abuse, loneliness, recent loss, previous suicide attempt, unrelenting pain and physical disability. Protective factors include strong ties to social and religious support networks. A thorough suicide risk assessment involves not only stated suicidal wishes but also behaviours indicating hopelessness and intention to end one's life. Collaborative assessment that involves other team members (e.g. family members, nurse, social worker) and prompt treatment of depression may reduce the risk of suicide.[20] Novel interventions (e.g. depression care managers, education of primary care providers on assessment and management of suicide and incorporation of such education into clinical practice) in community-based primary care offices can reduce suicidal risk regardless of depression severity.

Elder abuse

Older men and women of all socioeconomic and ethnic backgrounds are vulnerable to abuse and neglect and most often it goes undetected. Physical abuse is most recognizable, yet neglect is most common. Psychological and financial abuse may be more easily missed. Abused older adults are more likely to be physically dependent, cognitively impaired and have mental health problems than their non-abused counterparts. Although one in four vulnerable older persons is abused, only a small proportion of this abuse is currently reported. Most HCPs underestimate the prevalence of elder abuse. Asking older adults and their caregivers about abuse is probably the single most effective detection strategy. High index of suspicion combined with awareness of risk factors (e.g. cognitive impairment) and clinical manifestations (e.g. bruises) allows clinicians to provide early detection and intervention for abuse and neglect. Interventions that teach HCPs about the management of abuse by face-to face training rather than giving written information is recommended in order to increase the knowledge about elder abuse among HCPs.[21] Interdisciplinary collaboration between physicians, social workers and mental health professionals is crucial to detect and manage elder abuse.

Other common mental health problems in older adults

Psychological, behavioural and cognitive adverse effects of commonly prescribed medications and OTC drugs in older adults are prevalent and, in most instances, predictable and preventable. Drugs with significant anticholinergic properties (e.g. diphenhydramine), benzodiazepines and opiates are the usual suspects. Insomnia is prevalent in older adults. However, few mention their sleep problems to their primary care providers and most self-medicate with OTC medications. Many OTC sleep aids (such as diphenhydramine) have considerable psychiatric adverse effects (e.g. delirium). Sleep complaints in all older adults should be taken seriously and thoroughly evaluated to identify serious but eminently treatable conditions such as sleep apnoea and restless leg syndrome. Non-pharmacological interventions are first line in the treatment of chronic insomnia. These include improved sleep hygiene, cognitive behavioural interventions, bright light therapy, regular exercise and dietary changes (e.g. avoiding caffeine). Pharmacotherapy should be limited to short-term use of agents least likely to cause daytime sedation such as zolpidem, zaleplon and eszopiclone. Some older adults with chronic insomnia may benefit from these agents and also ramelteon. Personality traits that have been found frequently to affect the prevalence, course and prognosis of mental health disorders include neuroticism (tendency to experience negative emotions and emotional instability), extroversion (disposition toward sociability, positive emotions, dominance, high activity level), openness to experience (interest in new things, ideas and courses of action), agreeableness (deference, acquiescence, amiability, trust) and conscientiousness (diligence, reliability, organization,

goal striving). Evaluation of these traits may help tailor treatment interventions to patients' strengths and weaknesses and thereby improve outcomes. For example, higher neuroticism and low conscientiousness confer a higher risk of depression higher extroversion may enhance the odds of accessing specialty mental health services, higher openness may raise the likelihood of acceptance of innovative interventions such as meditation, higher agreeableness may improve odds of smoother transition to LTC facilities and higher conscientiousness may reduce the risk of dementia through better management of cardiovascular risk factors.[22]

Special populations in geriatric psychiatry

LTC residents

Mental health disorders account for at least half of the morbidity among the LTC population and are the prime reason for admission to LTC facilities. Behavioural and psychological symptoms of dementia (BPSDs) are the most common psychiatric problems in nursing homes. Education and training of all healthcare providers working in LTC facilities in assessment of psychiatric symptoms and their management with evidence-based psychosocial environmental and when necessary pharmacological interventions are key to improving the quality of life of LTC residents.

Ageing ethnic minority groups

It is estimated that by 2060, a majority of Americans will be 'ethnic minorities', and this increase will be most pronounced for Latinos and African Americans. At present, these groups have higher than average mental healthcare needs compared with others and this seems to result from income disparities and certain behaviours and attitudes that may be culturally related. Regarding healthcare services and, in particular, mental health services, many of these groups may be better served by providers who understand the culture and by systems that are closely aligned with community needs. Unfortunately, disparities in the provision of care to racial and ethnic minorities remain. These inequalities translate into inferior outcomes in these populations, especially in the ageing ethnic minority groups.

Older adults visiting the Emergency Department (ED)

The prevalence of mental health problems (especially alcohol abuse, depression and delirium) in older adults visiting EDs is high. Thus, screening for depression, alcohol abuse and delirium for all elderly persons visiting the ED is recommended. Brief interventions to address these disorders in the ED, such as notification of the PCP and home health providers, and referrals as needed may improve outcomes (e.g. reduced risk of functional decline).

Older prisoners

Older prisoners are the fastest growing segment of the population in US federal and state prisons. It is increasingly recognized that older prisoners have a higher burden of mental health, physical health and social problems, in addition to different mental health needs than the mainly adult male population within prisons. Up to 20% of inmates older than 55 years have a significant mental illness.[23] Depression, guilt, worry and psychological stress are common. Older inmates also express stress of being away from their families, the stigma associated with their crime and depression related to the possibility of dying in prison as some of the largest factors in their problems with emotional wellbeing. Ethnic minorities are over-represented in prison populations. Involving clinical faculty and staff from academic medical centres to provide healthcare (including mental healthcare) to the ageing prison population can produce significant improvements in access to care and health outcomes. Thousands of older and medically frail prisoners are being released early from prisons following a court-ordered inmate reduction programme. Many of these older inmates will need immediate care at hospitals, dialysis units and mental health units and their first stop in freedom may be the ED.

Caregivers

Many older adults find themselves in the role of caring for their spouse or partner with dementia or older children with disability (e.g. mental retardation). Caregiving can take a toll on the mental health of caregivers and has been associated with an increased risk of depression and functional decline. Caregiving involves learning to 'bend without breaking'. Transition to institutional care is particularly difficult for spouses, almost half of whom visit the disabled spouse daily and continue to provide help with physical and emotional care during their visits. Symptoms of depression and anxiety often do not diminish after institutional placement, use of anxiolytic medications by caregivers increases and nearly half of the caregivers are at risk for clinical depression following placement of their loved one in LTC facilities. Clinical interventions that prepare the caregiver for a placement transition and treat their depression and anxiety following placement are recommended. Healthcare providers must help families work towards effectively coping with the disease in their family member, decreasing the harmful effects on the family and keeping family conflicts to a minimum. Interventions such as counselling, support groups, psychoeducational groups, training in contingency planning, respite services,

skills training and family-directed treatments can alleviate caregiver stress, prevent caregiver depression and improve coping skills.

Oldest old

Oldest old refers to the 85 years and over age group, which is the fastest growing age group in the USA. This group has not been well studied and therefore is poorly understood by psychiatrists.[24] Although function varies widely among the oldest old, many quickly develop a serious decline in their cognitive and physical health, which in turn causes emotional suffering. This group also experiences loss of spouse and friends due to death and disability and therefore are at risk for bereavement- and depression-related morbidity and mortality. The boundaries between psychiatry and medicine become inextricably blurred at the most advanced ages. Once older people experience a serious general medical and/or psychiatric illness, physical, mental and social impairments coalesce and cascade, resulting in disability and premature death unless multimodal interventions are put in place. Oldest old patients receiving collaborative depression care were found to have a lower rate of long-term treatment response and complete remission in the long run compared with younger old.[25] Centenarians are proportionally the most rapidly growing segment of the oldest old. The majority of centenarians are in remarkably good emotional and cognitive health until the last few years of their life.

Palliative and end-of-life care

Conversations with patients and family about end-of-life care, the evaluation and treatment of suffering, including pain, depression, suicidality, anxiety and delirium, providing individual and family therapy to address conflicts, capacity determination, advance care planning, withholding life-sustaining treatments, palliative/hospice care and management of terminal agitation are some of the key areas where geriatric psychiatrists and other health professionals can contribute to a dignified and peaceful final phase of life for older adults.

Geriatric psychopharmacology

Older adults are substantial users of psychopharmacological agents. About 12–15% of older adults living in the community and up to 75% of LTC residents receive psychotropic medications at some point in their lives. All psychotropic agents should be prescribed judiciously and only for severe and/or chronic mental health symptoms because of the potential for serious adverse effects and even death associated with many psychotropic agents. Therefore, PCPs caring for older adults need to have a comprehensive knowledge of the risks and benefits of commonly prescribed psychotropic drugs (e.g. SSRIs, benzodiazepines, atypical antipsychotics). Table 81.5 summarizes the principles of psychopharmacotherapy in older adults. Benzodiazepines, commonly used for the treatment of anxiety and insomnia, are the most frequently prescribed psychotropic agents in older adults. Because of their potential to cause cognitive impairment and problems with balance which may increase the risk of falls and fractures, their use should be restricted to short-term treatment of incapacitating anxiety symptoms and/or insomnia.

Table 81.5 Principles of psychopharmacotherapy in older adults.

1	Perform a thorough evaluation prior to prescription of psychotropic agents
2	Optimize conditions for successful psychopharmacological outcomes: a Reduce anticholinergic burden b Discontinue unnecessary drugs c Check liver and kidney functions prior to initiation of psychopharmacological therapy
3	Identify goals of psychopharmacological therapy and discuss them with the patient prior to initiation
4	Provide education regarding the importance of compliance and adverse effects to look for
5	Select a psychotropic agent based on evidence to date, patients' physical health conditions, risk of drug–drug interactions and response to previous agents that may have been tried
6	Start low and go slow
7	Give an adequate dose for an adequate duration
8	Combine psychopharmacological therapy with psychotherapy and or other psychosocial interventions
9	Monitor for adverse effects and drug–drug interactions
10	Measure response to treatment
11	Discontinue psychotropic agents if there is no response
12	Introduce/change one psychotropic agent at a time

Electroconvulsive therapy

Older adults constitute more than one-half of patients who receive ECT for the treatment of depression. ECT is an underutilized treatment options despite its relative safety and high effectiveness for relieving depression in older adults. Although ECT is often considered only when depression is life threatening (e.g. the patient is suicidal, not eating), it should be considered a first-line option in all patients with severe depressive symptoms, especially in the presence of psychotic symptoms. The efficacy of ECT does not diminish with advancing age but the seizure threshold increases.

Psychotherapy and other psychosocial interventions

Later life is increasingly seen as a time of vitality during which individuals can expect to explore and develop their potential. Psychotherapy can foster this. Society has made available social services and living options that did not exist a few decades ago. Although emotions are vital ingredients of all the therapies, focus is best directed at functional outcomes. Psychotherapeutic approaches in older adults need to be dynamic and sensitive to the existential issues of loss, dependency and change of status, yet fully aware of opportunities for growth and vigour. Psychotherapy can play a vital role in the relief of suffering for older adults, their families and palliative care staff. Existential anxiety of facing death in old age can also be addressed during psychotherapy. The use of psychotherapy in combination with medication can improve long-term outcomes and decrease disability in elderly depressed patients. The task in later life is the acceptance of life as a finite and almost completed product and, therefore, an acceptance of mortality. Usually, this is accomplished without help being needed from psychiatrists or psychotherapists. The burden of caring for older patients near death or actually dying requires an acute awareness and unusual flexibility on the part of the therapist. When the focus is changed to quality of life and decreasing suffering, even for just a few days, all mental health interventions in end of life become meaningful. Regardless of disability or age, hope and dignity can be maintained to the end. Cognitive behaviour therapy, interpersonal therapy, problem-solving therapy and family therapy appear well suited to addressing many physical, interpersonal, social and financial problems among older adults with depression and anxiety. Families are such important components of older adults' lives that they offer a powerful locus for intervention, in addition to powerful support for individual interventions. Clinicians need to 'think family' as they provide mental and physical health services to older adults, as older adults are highly likely to be intensively embedded in a family support and care structure.

Spirituality and geriatric psychiatry

A growing literature links religious participation and spirituality with better mental health among older adults. Religiosity/spirituality may (a) provide a sense of meaning or purpose that buffers stress and assists with coping; and (b) provide a network of like-minded persons who can serve as social resources and promote the development of psychological resources, including self-esteem and a sense of personal growth. Clinicians have a moral obligation to address patients' spiritual concerns. In considering the spiritual dimension of the patient, the clinician is sending an important message that he or she is concerned with the whole person. This enhances the patient–physician relationship and is likely to increase the therapeutic impact of interventions. Referring older adults suffering from depression, pain or other serious symptoms to chaplains or to their own personal clergy should be routinely considered.

Prevention in geriatric psychiatry

With the rapidly growing number of elderly individuals at risk for depression, delirium and dementia, finding ways to prevent these syndromes is a public health priority.[26] Older adults with multiple risk factors (e.g. chronic pain, stroke, dementia, hearing and vision deficits, residing in an LTC facility) may be considered a target population for prevention programmes. As we continue to understand risk factors better, it may be possible to personalize depression, suicide and dementia prevention. Other targets for prevention include premature institutionalization and alcohol or medication misuse. Table 81.6 highlights some of the evidence-based prevention interventions.

Best practice models for geriatric psychiatry services

Service needs of older adults with psychiatric disorders are complex. Older adults with psychiatric disorders commonly face, in addition to persistent symptoms, increasing medical morbidity, dwindling financial resources and social impoverishment. In addition, older adults are victims of a culture that has stigmatized both mental illness and advanced age. Older adults with psychiatric disorders are more susceptible to stigmatization than younger adults and therefore less likely to seek help. Older adults are less likely than younger persons to self-identify mental health problems or seek specialty mental health services. This problem is further compounded by family members and professional providers who share the misperception that mental disorders such as depression and dementia are a 'normal part of ageing'. Without addressing stigma, systemic reforms designed to improve access are unlikely to be successful. The use of community-based, multidisciplinary, geriatric mental health treatment teams is one of the ideal models of psychiatry service delivery in the community.[34] Hospital-based geriatric psychiatry consultation–liaison services are also recommended to meet the complex mental health needs of hospitalized older adults. Geriatric psychiatry subspecialty care for older adults needing treatment in an inpatient psychiatric unit appears to be associated with distinct clinically relevant assessment and treatment advantages (such as complete medical work-ups, structured cognitive assessment, ageing sensitive aftercare referral and monitoring of psychopharmacological side effects and blood levels) over general

Table 81.6 Examples of evidence-based prevention in geriatric psychiatry.

Interventions	Potential outcomes
Non-pharmacological multicomponent interventions[19]	Prevention of delirium
Telemedicine[27]	Prevention of psychiatric admissions from LTC facility
Family intervention[28]	Delay in institutionalization of patients with dementia
Exercise plus behavioural management[29]	Reduced disability in patients with dementia
Caregiver counselling and support[30]	Prevention of caregiver depression
Depression care managers in primary care[20]	Prevention of suicide
Comprehensive nutritional treatment[31]	Prevention of weight loss in patients with dementia
Exercise[32]	Prevention of depression
Adult day programme[33]	Reduced risk of accelerated cognitive decline associated with nursing home placement

psychiatry care. Best practice models for mental healthcare in LTC facilities include routine presence of qualified mental health clinicians in the nursing home, interdisciplinary and multidimensional approaches using innovative techniques in training and education and consultation and feedback on clinical practices. Model services to meet the growing needs of all older adults with psychiatric disorders will require a multidisciplinary approach to treatment, encompassing both the traditional models of psychiatric treatment and treatments that focus on medical, cognitive and social arenas.

Although there is considerable underutilization of mental health services by older adults in all settings (primary care, hospital, long-term care, home health, rehabilitation), older adults who receive treatment report benefiting from services at least as much as their younger counterparts. The President's New Freedom Commission on Mental Health urged the adoption of evidence-based practices (EBPs) across the lifespan and its Subcommittee on Older Adults identified the dissemination and implementation of EBPs as one of the most important initiatives for improving quality of care for older persons with mental disorders.[1]

Long-term care homes

Visionary and determined people are reinventing LTC facilities. These individuals believe that each of us, no matter how old, sick, frail, disabled or forgetful, deserves to have a loving home – not a facility. These individuals have pioneered long-term care homes (LTCHs) to replace long-term care facilities (LTCFs). Such LTCHs make the quality of life of their residents life affirming, create a culture that rekindles the human spirit and mend the frayed social fabric of our current society. Such transformational change is needed not only in LTCFs but also in the entire culture of ageing. There are several remarkable LTCHs led by people with vision and determination and staffed by compassionate, creative and competent individuals. Residents and staff members of such LTCHs have more friends than restrictions and rules to follow. Such LTCHs know that the single most important thing residents and caregivers (family and professional) value – more than good food, good medical care or clean facilities – is the warmth of a caring relationship. Such LTCHs sustain their high-quality care through relentless adherence to person-centred care (PCC). We need to give homes that have adopted PCC credit and create incentives and training for every home to begin its own journey towards PCC. An ideal LTCH not only becomes a home of choice in the community, but also reduces staff turnover and the cost of healthcare (e.g. reduced hospitalizations at the end of life).

Geriatric psychiatry in primary care offices

Approximately one-third of older primary care patients have significant mental health problems. There is high comorbidity of mental health disorders in older adults with medically unexplained symptoms. Utilization of herbal and nutritional compounds is very high (up to 30%) in older adults with mood disorders. Therefore, HCPs in primary care need to assess f routinely or their use, particularly with respect to potential drug–drug interactions. Many older adults prefer to receive mental health services in community-based settings (especially in their PCP offices) and home-based settings (e.g. home visits including psychotherapy for frail older adults). Care management models that integrate mental health providers (e.g. trained social workers) into the primary care setting to provide same-day mental health services show promise in enhancing access to high-quality mental healthcare.

Academic detailing, which consists of brief one-to-one educational sessions coupled with provider-specific feedback on treatment practices, is effective in influencing the practice behaviour of PCPs and can be used to improve the management of psychiatric disorders in primary care.

Successful ageing

Emotional and cognitive health as it pertains to the older adult should be defined not just as the absence of disease, but also as the development and preservation of the multidimensional emotional and cognitive structures that

allow the older adult to maintain social connectedness, an ongoing sense of purpose and the abilities to function independently, to recover functionally from illness or injury; and to cope with residual functional deficits.[35] In daily life, the domains of emotional and cognitive health are inseparably linked. Therefore, promoting emotional wellbeing should be conceptualized hand in hand with promoting cognitive wellbeing. The ageing human brain has a surprising capacity to maintain plasticity. Although usually under-emphasized, positive personality changes, such as better tolerance, regulation of affect and ability to appreciate different points of view, occur with ageing and can contribute to successful adjustment and high quality of life. Older adults as a whole do not have more psychiatric disorders than younger adults, they do not see themselves as sick even when they take three to eight different medications, their fear of death declines and their spirituality and serenity increase. Improving levels of education may have a positive impact on late-life emotional and cognitive wellbeing. Researchers to date have identified many predictors of successful ageing (such as absence of alcohol abuse and of cigarette smoking before the age of 50 years) that are to a large extent under the individual's own control. Stable marriage and adaptive defences are also predictive of successful ageing, subjective satisfaction and objective mental health. Among factors outside the individual's control, only depression before the age of 50 years was a significant predictor of mortality, medical morbidity and sadness during late life. Older adults with strong feelings of personal control and self-efficacy (that is, the personal conviction that one can successfully execute behaviours required in novel or stressful situations) are more likely to cope successfully with late-life challenges and, consequently, more likely to maintain a high level of emotional wellbeing. The presence of a spiritual belief system has also been correlated with decreased depression, faster recovery from illness and increased longevity in later life. SECA may involve optimal balance between functions of phylogenetically more primitive brain regions (limbic system) and newer ones (prefrontal cortex).

An extract from a poem by the Indian poet Rabindranath Tagore reflects the attitude that many older adults who age successfully have toward life, death and disease. It is time geriatric psychiatry pays as much attention to health promotion as to disease.

On fear of death

Let me not pray to be sheltered from dangers but to be fearless in facing them.

Let me not beg for the stilling of my pain but for the heart to conquer it.

Let me not look for allies in life's battlefield but to my own strength.

Let me not crave in anxious fear to be saved but hope for the patience to win my freedom.

Grant me that I may not be a coward, feeling your mercy in my success alone; but let me find the grasp of your hand in my failure.

Rabindranath Tagore (in *Fruit Gathering*).

Future research

The DSM-IV TR has significant limitations relative to its utility in older adults with mental health problems. Future research needs to overcome these limitations. The most prevalent activity throughout our lives is work. Future studies need to clarify whether retirement has detrimental effects on emotional and cognitive wellbeing, especially for individuals who do not have resources to maintain a high level of activity and social participation. Only in the last few years has attention been paid to studying preserved emotional and cognitive health as an outcome in older adults. Future research needs to identify validated instruments to measure these outcomes. There is also an emerging realization that whenever emotional disorders (e.g. depression) and cognitive disorders (e.g. dementia) occur together, they worsen each other. More research is needed to clarify these complex interactions and identify interventions that prevent accelerated decline in function and premature death.

Key points

- Psychiatric disorders in older adults are prevalent and eminently treatable.
- Comprehensive assessment, an interdisciplinary approach and holistic multimodal interventions are the hallmarks of geriatric psychiatry.
- Evidence base is most developed for interventions addressing depression and dementia in older adults, although effective treatments and service models have been identified for a variety of psychiatric disorders in older adults.
- Overcoming barriers such as stigma, inadequate reimbursement for psychiatric services, lack of geriatric expertise, fragmented care and lack of integration of primary care and mental health services is crucial to preventing the upcoming crisis in geriatric psychiatry services.

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CHAPTER 82

Organization of services in geriatric psychiatry

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Introduction

Old age psychiatry is a relatively young specialty of psychiatry: the first pioneers of 'psychogeriatrics' began to develop specialist services for older people in the UK in the 1960s and 1970s. Early service principles included:

- a comprehensive age-related catchment area service
- assessment at home before admission by a senior member of the team
- diagnosis followed by active treatment
- team working
- close liaison with GPs, geriatricians and social services.

In 1989, old-age psychiatry was recognized as a specialty by the UK Department of Health and by the millennium the Royal College of Psychiatrists recognized over 350 specialists in the psychiatry of old age. In 2004, the number of old age psychiatrists was given as 444[1] and in September 2007 there were 543 old age psychiatrists (representing 510 full-time equivalents) in England alone (see http://www.cfwi.org.uk/).

It is useful to revisit the reasons why old-age psychiatry first developed. Within an all-age adult psychiatry service, older adults were not receiving the dedicated care and attention they deserved, as they were in competition with younger adults for attention and resources. Younger psychiatric patients present high-profile risks and work with young people carries higher kudos, perhaps because they are economically active and conform to accepted ideals of attractiveness. This ignores the enormous contribution which older adults make to society: most voluntary organizations would disappear without the input they provide, many continue to work long after retirement age, many take up or continue roles as carers (to younger people, people with learning disabilities, to other elders). Others continue to make their wisdom and talents available to the rest of society.

Looking beyond these ageist and attitudinal obstacles, mental illness in late life offers additional challenges as it is often complicated by comorbid physical illnesses, the physical and psychological changes associated with ageing, and/or by the coexistence of cognitive impairment. These attributes demand special skills and organization of the mental health professionals who aim to provide a service orientated to the practical needs of many elders.

The National Service Framework for Older People (NSF-OP: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4003066) set out a service model for a comprehensive mental health service for older people. Components of the model service were to include:

- mental health promotion
- early detection and diagnosis
- assessment and treatment
- support for carers
- specialist mental health services, to include acute admission and rehabilitation beds, day hospitals and memory clinics, domiciliary and outreach care and outpatient/community clinics.

The NSF-OP was warmly received by many old age psychiatrists as it embedded mental health as integral to the health of older people and its core principles ('rooting out age discrimination' and 'person-centred care') are potentially powerful influences for positive change in older people's mental health.

The National Service Framework for Mental Health (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH-4009598) had been less warmly received as it excluded older adults and focused on services to working aged adults. Monies and developments associated with the NSF-MH therefore excluded older adult services and led to expansion of working-aged adult mental health services at the expense of services to older adults. The NSF-OP stated that older people with severe mental illness would require the packages of care set out in the NSF-MH, but this requirement went largely unnoticed at the time.

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Developments in the UK 2005–2010

Over the 5 years between 2005 and 2010 much has happened. Policy never stands still. Securing better mental health for older adults (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4114989) and Everybody's Business (http://www.nmhdu.org.uk/silo/files/six-key-messages.pdf) set out useful details about the structure and aims of OPMH services. Our Health, Our Care, Our Say (http://www.behfuture.nhs.uk/archive/docs/appendix_2.pdf) highlighted the need to improve the health and care of people with complex long-term conditions and to provide good local community facilities. It recognized the need for a national framework for NHS continuing and nursing care and clarity regarding what the NHS will provide for those with the most complex long-term care needs – this includes those people who need long-term care for mental health problems in late life. The NSF-OP was followed by the dignity in care campaign (see www.dhcarenetworks.org.uk/dignityincare/DignityCareCampaign/), which straddles mental and physical healthcare services.

Alongside these developments sit professional initiatives. Useful professional documents produced by the Royal College of Psychiatrists include the Faculty of Old Age Psychiatry report Raising the Standard (www.rcpsych.ac.uk/PDF/RaisingtheStandardOAPwebsite.pdf), the report on older adult liaison services called Who Cares Wins (www.bgs.org.uk/PDF%20Downloads/WhoCaresWins.pdf), a report produced jointly with the Alzheimer's Society on services for younger people with dementia (www.rcpsych.ac.uk/publications/collegereports/cr/cr135.aspx), a report on transitions between general psychiatry services and older people's mental health services (www.rcpsych.ac.uk/files/pdfversion/CR153.pdf) and an updated report on services to ethnic elders (www.rcpsych.ac.uk/files/pdfversion/CR156.pdf).

The Mental Capacity Act of 2005 (www.opsi.gov.uk/acts/acts2005/ukpga_20050009_en_1) had far-reaching implications in England and Wales for the care of people who may be incapable of making decisions. It changed the legal context: there is an obligation to take 'all practicable steps' to help the person make their own decision and to consider whether the outcome could be achieved in a less restrictive way when doing something to someone or making a decision on their behalf. The Act was modified in 2007 to introduce safeguards for very vulnerable people at risk of being deprived of their liberty.

Meanwhile, social care has developed a new emphasis on personalization, which is sometimes seen purely in financial terms as putting people in charge of how money is spent on their care, but, in fact, potentially embraces a much wider move towards giving individuals more control and choice in respect of their support services. New Horizons (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_109705) brings together a life course approach, which sees older people's mental health brought together with mental health at other stages of life and personalization.

With regard to dementia services, this period has seen the controversial 2009 updating of NICE's Technology Assessment of the anti-dementia drugs (http://guidance.nice.org.uk/TA111), which accepted that the anti-Alzheimer's drugs are clinically effective but restricted their use (on the grounds of dubious cost-effectiveness) to people with moderate dementia, resulting in a storm of protest in the media. The protests were muted somewhat by the commonsense approach of the dementia guideline (www.nice.org.uk/nicemedia/pdf/CG42Dementiafinal.pdf). Since then, an ambitious National Dementia Strategy (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_094058) has been introduced, but in the prevailing economic climate it will be surprising if the strategy achieves its aspirations. Dementia 2010 (www.dementia2010.org/reports/Dementia2010Full.pdf) has recently highlighted how important it is for the country, financially and in human terms, to face the challenges posed by the dementias, which are costing the UK economy more than cancer and heart disease combined.

Changes in practice have occurred alongside these initiatives. Some services have subdivided into inpatient and community services or sponsored specialist teams for liaison mental health, home treatment[2,3] or even forensic problems.[4] There are some enthusiasts for specialist 'dementia-only services', a notion supported by some charities and managers. We would counsel the preservation and enrichment of services which are catholic in their acceptance criteria and comprehensive in their coverage.

The ageism saga continues

The exclusion of older people from the NSF-MH in 1999 was regarded by some as ageist and the New Horizons initiative (www.dh.gov.uk/en/Healthcare/Mentalhealth/DH_209) has since recognized that old-age psychiatry is firmly part of the family of psychiatry. However, there are hazards ahead: it is equally ageist to deny that older adults have special needs to which services should be sensitive and in dealing with which service organization and response must be competent. What is right for adults of working-age will not always be right for older people. Older people need services which are designed to meet their particular and often complex needs. These are not confined to dementia, so services should encompass the whole range of mental disorders of late life for a number of reasons:

• The distinction between depressive disorders and the dementias is not a clearly defined boundary. Many people present to services with a mixture of symptoms raising the classical old-age psychiatry conundrum – is this depression or is this dementia? (it may of course be both).
• Older adults with other mental health problems and without a dementia have special needs in service terms and should receive appropriate specialist help.
• Other mental illnesses also overlap with the dementias, for example, anxiety disorders, paranoid states.

Hence the issue of age discrimination in mental health is a challenge for services, which must be tailored to need and not to rigid age cutoffs or politically correct prejudices. This is an important principle in service planning and delivery.

Services

Community old-age psychiatry

Community treatment

One of the early principles of old-age psychiatry was assessment at home by a senior member of the old-age psychiatry team.[5] This led on to the concept of a community clinic[6] and many services carry out the majority of their assessment, treatment and follow-up by seeing people in their homes, coordinating the activity of different disciplines using IT support and close liaison between team members. Community treatment for older people involves close working with social services (particularly with day centres for older adults and domiciliary services) and voluntary organizations and close links between the CMHT-OP and places where older adults are resident, including sheltered and extra-care housing and the residential and care home sector.

Early detection and diagnosis: interface with primary care

The majority of people with mental health problems in late life are never seen by a specialist service. Many will remain unrecognized even when they have contact with primary and social care services (for more details, see www.nao.org.uk/publications/0910/improving_dementia_services.aspx).

Family doctors are, however, well placed to identify cognitive problems and mood disorders early, to provide people with information and to introduce them, where necessary, to further investigations, treatment and support. Those working in primary care see many elders with physical problems regularly and this gives the opportunity to assess and monitor the person's mental health in a familiar setting. An established relationship with their family doctor or practice nurse may also help an individual to accept the need for referral to specialist services for assessment, treatment or support or to social services or voluntary organizations. The family doctor is an essential and central person in care coordination. A useful opportunity for early detection presents when people are being seen in primary care for other reasons. For example, people at high risk for arteriosclerosis are also at high risk for developing a vascular dementia, and family doctors screen people routinely for cardiovascular disease. Those who are identified as at high risk are examined regularly and have renal function and lipid levels checked. Some family doctors add a cognitive test to the cardiovascular assessment and use this opportunity to detect cognitive problems. This practice is now rewarded within the QOF system (see www.qof.ic.nhs.uk).

One of the milestones set out in the Older People's NSF was that Primary Care Trusts (PCTs) were required by April 2004 to ensure that every general practice was using a protocol agreed with local specialist services for the diagnosis, treatment and care of older adults with depression or dementia. Protocols for the treatment of people with Alzheimer's disease aimed to set out physical investigations and cognitive testing which could be carried out in primary care, in order to facilitate early detection and rapid access to anti-dementia drug treatment if appropriate. Tucker *et al*.[7] found that fewer than 50% of their responding consultant old-age psychiatrists reported that GPs were using protocols for the care of people with depression or with dementia. Where are the protocols now?

A great deal of research is currently being directed towards improving the performance of primary care in identifying and caring for people with dementia.[8] Some specialist services have developed formal links with primary care.[9]

Community mental health teams for older people (CMHT-OP)

The NSF-OP set out who should be core members of the CMHT-OP: this included community mental health nurses, consultant old-age psychiatrists, clinical psychologists, social workers and occupational therapists. A range of other disciplines were listed as needing to have agreed working and referral arrangements with the team but not working as full members of it. One of the big issues for a CMHT-OP is that of 'integration'. In this context, integration usually refers to the integration of health and social care (for more information, see http://its-services.org.uk/silo/files/integrating-opmh-services.pdf). The Durham mapping project pilot in older people's mental health services used four main criteria for an integrated CMHT-OP:
• The team should include interagency multidisciplinary staff involving health and social services.
• It should provide integrated assessment, care planning and care coordination.
• It should use shared recording systems and IT, supporting both the Care Programme Approach (CPA) and the Single Assessment Process (SAP).

• There should be a single point of entry to specialist mental health assessment.

Integration remains an issue today, although, along with protocols, it has become less fashionable. A 'single point of access' has become a must-have for many managers who are rushing to introduce it despite feedback from a number of localities that it introduces a new raft of service problems.

How teams work in relation to team members' responsibility is another continuing question. This became increasingly important because of high consultant psychiatrist vacancy levels in the UK (running at around 12–14%) with associated problems of recruitment and retention, coupled with evidence that consultants were overburdened and stressed.[10] An initiative called New Ways of Working (see http://www.newwaysofworking.org.uk/component/option,com_docman/task,cat_view/gid,214/Itemid,412/) claimed to modernise mental health services by placing greater responsibilities on nurses and other non-medical staff. The aim has been to reduce pressure on consultant psychiatrists and to enable them to focus on more complex cases. Insensitive top-down insistence on imposing this model nationally and on including services for older people has not been appreciated.[11]

Specialist community teams

Some services for older people have claimed that there is an advantage in establishing specialist teams: examples include specialist home treatment teams,[2,3] crisis resolution and home treatment teams extended to cover older adults[12] and Care Homes Support teams (www.rcpsych.ac.uk/files/pdfversion/CR153.pdf). These initiatives are usually the product of opportunistic local service redesign and require rigorous objective evaluation. Most are conceived in the belief that they will enable more people to be treated in their own homes, thus avoiding hospital admissions and costing less.

Hospital

Hospital-based facilities

Acute inpatient beds

Community-orientated services need access to inpatient beds for the assessment and treatment of older people with a range of diagnoses who cannot be managed in the community. A small proportion will be detained under mental health legislation. The main distinction is between people who have an organic brain disorder and those with so-called functional disorders, the most common of which is depressive illness. Current thinking is said to support separate inpatient provision for people with organic brain disorders and those with other mental health problems in later life (www.audit-commission.gov.uk/health/nationalstudies/socialcare/pages/forgetmenot_copy.aspx). The distinction between the two is often neither clear nor absolute in practice, and flexibility and tolerance are needed when accommodating the changeable and complex needs of very ill/disturbed older people. It is not usually appropriate to care for older adults with complex needs on wards for younger adults. This would place them at risk and deprive them of the specialist nursing, medical and other care which they require.

Day hospitals

Day hospitals for older people are widely available across the UK, but the literature supporting their role is remarkably sparse. The Faculty of Old Age Psychiatry carried out a survey of old-age psychiatry day hospitals and published a report in June 2001 (see www.rcpsych.ac.uk/pdf/surveydayhospitals.pdf). Three-quarters of day hospitals operated a mixed service to people with organic and functional illnesses in late life. The study found that people attend day hospitals for a great many different reasons and for varying periods of time: over one-third of people attend for over 1 year. Carer support is a common feature of a day hospital service and some units aim to provide a respite service for people with dementia in association with particularly challenging behaviours which restrict their access to alternative sources of respite. Aims for an old-age psychiatry day hospital include the following:

• reduction of inpatient bed use by functionally ill older people
• prevention of admission: by supporting CMHTs in maintaining ill people in the community during crisis
• prevention of readmission through relapse prevention
• prevention of readmission through prevention of recurrence
• reduction of duration of an episode of inpatient treatment.

Outpatient clinics

For many services, the majority of activity takes place in the community using a community clinic model. Some older adults may prefer to be seen in a traditional hospital-based outpatient clinic. The hospital may also support specialist clinics, for example, clinics carried out jointly with geriatric physicians or neurologists, memory clinics or family therapy clinics.[13] Some outpatient clinics may be carried out in settings other than the hospital, for example, GP surgeries, day centres, nursing homes or residential homes.

Memory clinics

Memory clinics are imported from a North American tradition. Initially they were configured to attract people with mild memory problems who might become subjects of research, but they have spread in popularity and are seen to offer high-quality assessments, information, education and support to patients and carers.[14] Although

memory clinics are closely associated with anti-dementia drug treatments, they are also linked with psychosocial interventions. The National Dementia Strategy (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_094058) positions them as the preferred access point for assessment and specialist care, that is, preferable to the traditional community contacts of old-age psychiatry service.

Services to the general hospital

Older people are frequently admitted to hospital because of inter-current illness. Some will have pre-existing psychiatric problems; others may develop new mental health problems in association with their acute physical illness. All will require attention to the full range of their needs. Unhappily, the environment of large general hospitals is often less than helpful to frightened, confused old people (see http://alzheimers.org.uk/countingthecost). The pressure to move from assessment ward to treatment ward and out of hospital may compound their difficulties. Formal liaison psychiatry services did not, traditionally, take a major interest in older people and old-age psychiatry services often gave greater priority to patients in the community, thus leaving older people with mental problems on hospital wards to fall between the two services. This failing is being addressed by the development of old-age psychiatry liaison teams (see www.bgs.org.uk/PDF%20Downloads/WhoCaresWins.pdf)[15] and by broader initiatives within the organization of general hospitals encouraged by the National Dementia Strategy.

Intermediate care for older people with mental health problems

Intermediate care was conceived originally in response to the increasing demand for acute hospital services and aimed to promote faster recovery from illness, prevent unnecessary acute hospital admissions, support timely discharge and maximize independent living. After a decade of mixed experiences,[16] refined guidance (see www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@pg/documents/digitalasset/dh_103154.pdf) confirms its place within the spectrum of healthcare and emphasizes that people with dementia or other mental disorders should be able to access this service and its benefits.

Special groups

Elders with learning disability

People with a learning disability are much more likely to survive into their sixties and beyond now than was the case in the past.[17] People with learning disability may develop problems characteristic of late life earlier than the general population; those with Down syndrome are particularly at risk of Alzheimer's disease,[18] which requires skilful care in its terminal phases. Thus, older people with learning disability may have complex needs which cross the interface between old-age psychiatry, geriatric medicine and learning disability services. Good practice will often require that services work together to meet an individual's needs best.[19] Flexibility and trust are vital. Users and their families need to be clear about care plans, about who is taking responsibility for what and how they might be contacted. Commissioners need to ensure that this group is not neglected in service planning.

Early-onset dementia

The Alzheimer's Society[20] provided a charter for younger people with dementia and their carers in 1996. This supports early diagnosis, assessment and referral and access to specialist services. In 2000, the Royal College of Psychiatrists published a Council Report which recommended that each district should have a named consultant responsible for the service for younger people with dementia and that old-age psychiatrists should take the lead. A postal survey demonstrated that awareness of the report was comparatively high, but no area met all the report's recommendations. There was evidence of improvement in service provision and many respondents outlined plans for future development. Progress since then has been patchy and disappointing. The Council Report has been revised and updated (see www.rcpsych.ac.uk/publications/collegereports/cr/cr135.aspx). It recommends that commissioners should have:

- a named individual who takes responsibility for commissioning services for younger adults with dementia
- specific contractual arrangements for a specialized service for younger people with Alzheimer's disease and other dementias, including programmed time from a named consultant (usually an old-age psychiatrist).

People with enduring or relapsing mental illness

Those individuals who lived out their lives with chronic schizophrenia, manic-depressive psychosis, brain damage or personality disorders in large mental hospitals were often overlooked by the psychogeriatric services of the 1970s and 1980s. Closure of the large mental hospitals and changing expectations have meant that new generations of 'graduates' with a psychosis live within the community, often in hostels or nursing homes. They may have remained in touch with mental health services or drifted out of touch. They are at risk of neglect or misunderstanding or of falling into a gap between different services.[21] Their plight has been recognized and existing

guidance encourages all authorities to recognize them, discover their needs and agree the best arrangements for their care within the range of available local resources (see www.rcpsych.ac.uk/files/pdfversion/CR153.pdf).

People in residential and nursing care

Despite the emphasis on supporting people in their own homes and providing alternative and innovative housing solutions for older, frailer people, large numbers spend their last months or years in residential homes or nursing homes. In many residential homes, 40% or more of the residents have dementia and up to 20% are depressed or demonstrate other psychiatric morbidity.[22] Roughly half of the population with a diagnosis of dementia in the UK are in care at any one time. For most this is terminal care. The transfer of care from large, ill-sited, ill-equipped and poorly staffed mental hospitals to community-based residential homes nearer their families represents progress for many people, but there are continuing concerns over the quality of care available to residents and their quality of life. Scandals relating to hospital care in the past led to service improvement, yet scandals continue to be reported in a variety of institutional settings[23,24] (also http://www.elderabuse.org.uk/AEA%20Services/Useful%20downloads/Misc/CHI%20Rowan%20Ward.pdf).

Recent concerns have focused on the excessive use of tranquillizing medication and the lack of alternative treatment strategies, particularly in nursing homes specialising in the care of people with dementia (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_108303). It is essential that specialist services, both medical and mental health, take responsibility for the care of older people in the time of their greatest need, be this in residential or nursing homes or in the much diminished NHS continuing care sector.

Black and minority ethnic (BME) elders

The Royal College of Psychiatrists published a report on psychiatric services for BME elders in 2001 (see www.rcpsych.ac.uk/files/pdfversion/cr103.pdf). It was updated in 2009 (www.rcpsych.ac.uk/files/pdfversion/CR156.pdf) and made five main recommendations:

- Assessment and treatment should remain within mainstream psychiatric services.
- Continuing care services should be targeted at particular user groups.
- Services should endeavour to recruit a mix of staff reflecting the ethic mix of the local population.
- Good practice should be established and shared, perhaps using a website.
- staff should be trained in culturally sensitive issues.

There are already examples of good practice developing around the UK. In Wolverhampton alone there are several initiatives:

- Social services and health staff have jointly undertaken a course in basic Punjabi.
- Staff at a local day centre for Asian elders undertake exchanges with staff at the Resource Centre for older adults with mental health problems.
- A specialist CPN is employed to work with Asian elders presenting to old-age psychiatry.
- A support group for Asian carers of older adults with mental health problems has been established.

This experience must be multiplied many times around the country, as services increasingly address the needs of ethnic elders within their localities.

Patients' views and involvement

People with dementia and/or other mental health problems retain their individuality and views. The assumption that they are to be viewed as passive recipients of care (or neglect) has been strongly challenged recently. It is very clear that, until affected by the most severe stages of dementia, people want to (and should be able to) have a say in the life they are to lead. People are less afraid now to admit that they have a dementia and the emphasis on early diagnosis is likely to increase their demands. A number of publications have reported on subjective experiences of dementia, for example, Morgan.[25] Increasingly, services are encouraged to include patients within their planning and monitoring structures and the relevant charities sponsor and support patient action groups. Amongst these the Scottish Dementia Working Group is particularly impressive (see www.sdwg.org.uk/).

Carers

Carers in the UK have the right to an independent assessment of their needs (but not a right to services) under the Carers (Recognition and Services) Act of 1995 (see www.legislation.hmso.gov.uk/acts/acts1995/Ukpga_19950012_en_1.htm).

These rights have been further consolidated in England with the publication of the National Carers' Strategy (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085345). Many people who care for elders are themselves older adults (often spouses) and they may be stressed or have mental health problems. The National Institute for Social Work[26] identified 10 key requirements for carers (Table 82.1).

Thus carer support is a fundamental component of all aspects of service provision and carers are increasingly included in planning and monitoring services. The Alzheimer's Society (http://alzheimers.org.uk/) and Dementia UK: (www.dementiauk.org/) are charities strongly associated with supporting carers of people with dementia in England. They help individual carers, advise

Table 82.1 Key requirements for carers.

- Early identification
- Comprehensive assessment (including medical and social assessment)
- Medical treatment of treatable problems
- Prompt referral to other sources of help
- Information, advice and counselling
- Continuing support and review, preferably from a person known to and trusted by the carer
- Regular help with domestic tasks and personal care
- Regular breaks from caring (respite)
  Respite is seen as essential in sustaining informal carers of people with dementia and its impact and costs have been reviewed by colleagues at the University of York (see www.sdo.nihr.ac.uk/files/project/48-final-report.pdf)
- Financial support
- Access to permanent residential care when needed

and influence professionals and have the ear of government. There are equivalent international organizations. It is less easy to identify organizations specifically reaching out to families of people with other mental health problems in later life, but the general mental health charities and elder care charities do have special interest sections.

Additional responsibilities for geriatric psychiatry services

Health promotion

Mental health promotion is defined as 'any action to enhance the mental wellbeing of individuals, families, organizations and communities and a set of principles which recognize that: 'how people feel . . . (has) a significant influence on health'.[27] To promote mental health, rather than just treat mental illness, is a daunting challenge, yet aspects of mental health promotion are already incorporated into good service planning and operation. An approach which aims to promote health carries the potential for improving services and for improving the quality of life for people using those services. Mentality's briefing paper on evidence-based mental health promotion[28] set out a range of possibilities: opportunities for social and physical activities, access to information and practical help, volunteering and discussion and self-help groups are all linked with an evidence base showing a positive effect on mental wellbeing. The links between physical and mental health are also highly relevant to older adults who have factors known to predispose to vascular disorders; these are recognized to be associated with an increased incidence of dementia and mood disorders.[29]

Mental health professionals often encourage people to modify their lifestyle following an episode of mental ill-health, in order to improve their resilience. The challenge is to incorporate routine use of mental health promotion techniques into the design of clinical services and to promote health in those people who have an established dementia or an ongoing or recurrent functional mental health problem.

Training, education and continuing professional development (CPD)

Old-age psychiatry is one of the six specialties of psychiatry recognized within the UK National Health Service (General Adult, Old Age, Forensic, Child and Adolescent, Learning Disabilities and Psychotherapy). Specialist training in old-age psychiatry currently lasts 6 years: 3 years for core or generic training (as a Core trainee CT1-3) and 3 years for advanced training (as a Specialty Registrar ST4-6). Core training provides a range of experience across the whole of psychiatry and during this time a trainee prepares to take the examination for membership of the Royal College of Psychiatrists, which consists of three parts. The Clinical Assessment of Skills and Competencies (CASC) examination is taken after 30 months' experience in psychiatry and is required for entry into an advanced training programme. By the end of 3 years of training in approved and supervised placements and having passed the membership examination of the Royal College of Psychiatrists, a trainee who wishes to specialize in old-age psychiatry competes to enter a specialty training programme and then moves into advanced training, rotating through a series of approved and supervised placements, which will prepare them for independent practice as an old-age psychiatrist. After successfully completing their advanced training, trainees receive a Certificate of Completion of Training (CCT), which enables them to enter the General Medical Council's Specialist Register, a mandatory requirement for NHS consultants. Throughout their training, trainees undertake workplace-based assessments and are expected to develop research and audit skills and other special interests.

Once they start practice as independent specialists, learning does not stop; indeed, some might say that is when it really starts. Consultant old-age psychiatrists plan their CPD prospectively and in line with defined objectives throughout their careers. Many consultant old-age psychiatrists will take part in formal and informal education and teaching, of undergraduates studying medicine, of postgraduate doctors in psychiatry and perhaps related fields such as geriatric medicine and of a range of other professionals working in mental health and related fields. These activities will be included in their job plans and they may undertake additional training themselves in order to develop their skills as educators.

Research and audit

Research and audit are included in the training of old-age psychiatrists. Consultants will therefore have trained in the principles of research and audit and will be able to appraise scientific literature critically and use evidence-based treatments. Many will themselves engage in audit projects and clinical or scientific research while continuing to work as clinicians. In this they may be encouraged by involvement in a research network (www.dendron.org.uk).

Unfortunately, academic old-age psychiatry is under-developed and under-resourced. Perhaps this reflects the lack of priority given to older people's mental health in research funding generally: a recent report found that government and charitable spending on dementia research is 12 times lower than that spent on cancer research, despite the considerable cost of dementia to the country and the projected rising cost with projected population changes (see www.dementia2010.org/reports/Dementia2010Full.pdf).

Other issues

Legal framework

The legal framework within which services operate in England and Wales has changed with the introduction of the Mental Capacity Act (www.opsi.gov.uk/acts/acts2005/ukpga_20050009_en_1). This is particularly important to old-age mental health services since many older adult service users may be incapable of taking some decisions by virtue of a dementia or other severe mental illness. Services need to ensure that people are given the appropriate information to enable them to take out a Lasting Power of Attorney should they so wish and/or to make additional provisions through an Advanced Directive (www.direct.gov.uk/en/Governmentcitizensandrights/Death/Preparation/DG_10029683). After much discussion, the Mental Act of 1983 has been revised rather than replaced (www.opsi.gov.uk/acts/acts2007/ukpga_20070012_en_1).

Access to psychological therapies

The NSF-OP stated that a full range of psychological treatments should be available for older people with mental health problems; some years later, it appears that this aim has still not been achieved, although many memory clinics are reported to have links with psychological therapies. Evans[30] found that provision varied widely across the UK and was of unknown quality. Hepple[31] reviewed psychological therapies for older adults and stated that their slow development is due to ageism. Evans and Reynolds[32] found limited or no access to psychological therapies via older people's mental health services in some areas of Wales. Hilton[33] commented on government funding made available for the treatment of anxiety and depression which was targeted at adults of working age; she argued that the Human Rights Act has been largely ignored in the provision of older people's mental health services. It is likely that future cohorts of older adults will expect access to psychological therapies and that this aspect of service provision will need to respond to their demands. It will be interesting to see how recent moves towards age equality in health and social care (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_107398.pdf) impact on this and other areas of care provision.

Spirituality

Spirituality (and the need for services to address spiritual needs) has been increasingly recognized as an issue for services recently. There is research evidence that active involvement with faith organizations links to better health outcomes. Health and social care professionals now increasingly recognize that they should identify the spiritual needs of their patients/users and their family carers and work with colleagues who have expertise in faith and spirituality.

End of life Care

Mental disorders are associated with reduced life expectation. Dementia in particular can be conceived of as a slow-burn terminal illness.[34] The presence of psychological symptoms during the time that death is approaching is difficult for the individual and for their family and professionals caring for them. Death has begun to emerge from its status of taboo subject. An end of life strategy encourages a positive approach to death and dying, including death with dementia or other mental disorder (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_086277). The loss of continuing care beds from the NHS Mental Health Services has meant that even difficult deaths are dispersed between home, care homes and general hospitals. Collaboration between old-age psychiatry and local hospices may provide a more appropriate model of care within this framework.[35]

An international perspective

Specialist mental health services for older people had their origins in the UK and have developed there as a model to which other countries can aspire. This account of services is based on the British scene as it has evolved from its roots in the late 1960s[36]. The UK model has been adopted in differing degrees in countries influenced by Tom Arie's British Council courses or lectures and publications from pioneers of the 1970s. There is, however, no international consensus on how best to provide services for older people with

mental illness. The International Psychogeriatic Association (see www.ipa-online.org/) brings together professionals interested in improving geriatric psychiatry knowledge and services worldwide and enables people to learn from the different experiences in countries with widely differing healthcare contexts. Although we tend to think of dementia as being a problem for developed countries, improved life expectancy means that providing for the physical and mental health of older people is a global priority, growing in significance each year. In reality, most people with dementia live in developing countries[37] and older people's mental health is becoming increasingly important politically across the world as people recognize the potential future cost implications of providing services for older adults with dementia and other mental disorders. The 10/66 Dementia Research Group (see www.alz.co.uk/1066/) is part of Alzheimer's Disease International and is actively researching into ageing and dementia in low- and middle-income countries.

Conclusion

Old-age psychiatry has developed rapidly over the past 30 years in the UK and is a respected specialty with a distinctive community-orientated approach, a penchant for seizing opportunities and a tradition of attracting practitioners who are passionate advocates for older people with mental illness. Since its inception, there have been tensions in its relationships with general psychiatry and geriatric medicine and a lack of clarity about where it belongs – in services for older adults or with the rest of mental health? These tensions reflect the need for the specialty to cross boundaries and ensure that its staff and services are made available to older people with mental health problems wherever they might be. Another area of tension is the perceived split between the dementias and functional mental illness, but this highlights the need for an older people's mental health service to be inclusive in providing services across the range of mental illness in later life rather than expecting its users to fall neatly into one diagnostic category. Recently, some areas of psychiatry have suffered from a fashion for fragmentation and rigid access criteria. It is important to recognize that the strength of the specialty has been its inclusive, person-centred, collaborative and specialist approach, which must be valued and maintained within rapidly changing (and challenging) service contexts.

Key points

- Community services may now include various specialist teams.
- Hospital services operate with minimum beds and the assumption that a split between 'organic' and 'functional' beds is possible and useful.
- Memory clinics are regarded as a preferred first point of contact for those with cognitive problems and are likely to evolve further following the introduction of a National Dementia Strategy in England.
- General hospital care of older adults with a mental illness is an area of increasing focus. Alongside these developments, special groups in need of extra attention have been attracting interest.

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CHAPTER 83

Depression in later life: aetiology, epidemiology, assessment, diagnosis and treatment

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Introduction

Depression, the most frequent cause of emotional suffering in later life, is associated with significant losses in health-related quality of life.[1] Depression adversely influences the outcome of comorbid health disorders.[2–4] Depression is related to an increased risk of mortality.[5] Among older adults, there is also a high comorbidity with cognitive decline and depression.[6] Depression in the medically ill elder also has negative consequences to their caregivers, who are typically family members. A diagnosis of major depression in older medical inpatients is associated with poor mental health in their informal caregivers, who also are typically comprised of family members.[7]

Varieties of late-life depression

Formal diagnostic criteria for depression are derived from the symptom criteria in the *Diagnostic and Statistical Manual*, 4th edition (DSM-IV).[8] *Major depression*, the most common mood disorder, is diagnosed when the individual exhibits, for at least 2 weeks, one or both of two core symptoms (depressed mood and lack of interest in most activities) along with four or more of the following symptoms: feelings of worthlessness or guilt; diminished ability to concentrate or make decisions; fatigue; psychomotor agitation or retardation; insomnia or hypersomnia; significant decrease or increase in weight or appetite; and recurrent thoughts of death or suicidal ideation.[8] For the most part, depression is similarly experienced by older adults if there are no comorbid conditions;[9] however, subtle differences with ageing may emerge. For example, depression with melancholia (symptoms of anhedonia, non-interactiveness and psychomotor retardation or agitation) appears to have a later age of onset than non-melancholic depression in clinical populations.[10,11] Older adults often experience depressive symptoms associated with bereavement after the loss of a loved one, symptoms consistent with those of a major depressive episode. Major depression may be diagnosed if the depressive symptoms are present at least 2 months or longer after the loss.

Minor, sub-syndromal or sub-threshold depression is diagnosed according to the Appendix of DSM-IV in the instance that one of the core symptoms is present (sad mood or loss of interest in most activities) along with one to three additional symptoms.[1,8] Other operational definitions of these less severe variants of depression include a score of 16 or more on the Center for Epidemiologic Studies Depression Scale (CES-D) but not meeting criteria for major depression,[12,13] a primarily biogenic depression not meeting criteria for major depression yet responding to antidepressant medication[14] or a score of 11–15 on the CES-D.[15]

Dysthymic disorder is a long-lasting chronic disturbance of mood, less severe than major depression that lasts for 2 years or longer.[8] It rarely begins in late life but may persist from mid life into late life.[1,16,17] To be diagnosed with dysthymic disorder, the older adult must experience a depressed mood for at least 2 years along with two of the following symptoms: eating disturbance, sleep disturbance, low energy or fatigue, low self-esteem, poor concentration or difficulty in making decisions and feelings of hopelessness. Finally, other investigators have suggested a syndrome of *depression without sadness*, thought to be more common in older adults,[18,19] or a depletion syndrome manifested by withdrawal, apathy and lack of vigour.[1,20–22]

Depression among individuals with dementia is fairly common, so much so that recently a group of investigators proposed a *depression of Alzheimer's disease (AD)*. In persons who meet criteria for dementia of the Alzheimer's type, three of a series of symptoms that include depressed mood, anhedonia, social isolation, poor appetite, poor sleep, psychomotor changes, irritability, fatigue or loss of energy, feelings of worthlessness and suicidal thoughts must be present for the diagnosis to be made.[1,23]

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Depression in late life is frequently comorbid with physical conditions. When the depression derives from the physiological consequence of the medical condition, the disorder is diagnosed as *mood disorder due to general medical condition*.[8]

Depressive symptoms may also temporarily meet criteria for major depression in the midst of bereavement and acute adjustment disorders. The context of the depression therefore helps the clinician to determine whether a diagnosis of major depression should be made and treatment instituted or whether the symptoms will be expected to remit on their own when an appropriate time has elapsed. The clinician must remember, however, that what initially appears to be a case of bereavement or an adjustment disorder may evolve into major depression with time.

Epidemiology of late-life depression

Depressive symptoms are no more or less frequent in late life than in mid life.[1,24–26] Several large epidemiological studies have been conducted to assess the prevalence of affective disorders in older populations. Generally, among the elderly, the prevalence of major depression is ~1–3%[1,27,28] and reports of clinically significant depressive symptoms in community-dwelling elderly have been ~8–16%.[1,26,29–31] Further, among individuals aged 85 years or older, the incidence of major depression appears to increase among the oldest of old,[32] reaching ~13%.[33] However, this increased rate is explained by factors associated with ageing, including a higher proportion of women, more physical disability, more cognitive impairment and lower socioeconomic status.[34,35]

Higher rates of depression and depressive symptoms have been consistently found for women compared with men in the general population and for the elderly.[36,37] Whereas some studies of the elderly have found few racial differences in the frequency of depressive symptoms[29,38,39] or in the frequency of depressive diagnoses,[31,37,40] others have found African American elders to have a higher frequency of depressive symptoms than Caucasians.[41–44] Depressive symptoms may be greater in African Americans than Caucasians solely due to differences in socioeconomic status (SES).[45,46] Nevertheless, African Americans are generally thought by psychiatrists to have fewer depressive symptoms and are much less likely to be treated with antidepressant medications.[47,48] Some have also raised the issue of misclassification of African Americans as depressed.[49]

Comorbidity of depression with medical illness

Depression late in life often occurs within the context of physical impairment,[50] especially in the oldest individuals.[1,34] For example, in a study of patients hospitalized with acute myocardial infarction, investigators examined the degree of association between clinical depression and medical comorbidity and found that the adjusted odds ratios for having major depression increased linearly with medical comorbidity.[51] Depression also adversely influences the outcome of comorbid health disorders in the elderly.[1,2,52,53]

In a recent meta-analysis, chronic health problems were found to be a risk factor for depression among older adults.[54] The quantitative meta-analysis showed that, compared with the elderly without chronic disease, those with chronic disease were at higher risk for depression [relative risk (RR), 1.53; 95% confidence interval (CI), 1.20–1.97]. Compared with the elderly with good self-rated health, those with poor self-rated health were at higher risk for depression [RR, 2.40; 95% CI, 1.94–2.97).

We have found the perception that one's basic needs are not being met predicted future depressive symptoms in a highly controlled analysis. These results suggest that perception of inadequate basic needs, even when income and other known correlates of depression are controlled, is a strong predictor of future depressive symptoms.[55]

Depression and cognitive impairment

Depression is associated with both mild cognitive impairment[56] and dementia.[57] The prevalence of depression among the cognitively impaired has been found to range between 20 and 50%.[23,58,59] Depression among individuals with dementia may be more frequent in those with vascular diseases compared with those with AD.[60–62] Elevated rates of depression have also been found among individuals with dementia secondary to Parkinson's disease.[63a,64], Depression may signal the onset of AD and may represent prodromal signs of dementia.[65–67] Research suggests that depression initiated a glucocorticoid cascade that leads to damage of the hippocampus, a brain structure integral to memory, leading to subsequent cognitive decline.[68]

Major depression among those with dementia is associated with greater impairment of activities of daily living (ADLs), worse behavioural disturbance and more frequent wandering, even after adjusting for severity of dementia or comorbid health problems. Minor depression was also associated with non-mood behavioural disturbance and wandering.[69]

Course of late-life depression

Depression is a chronic and recurring illness.[70–75] In a meta-analysis[76] of the prognosis of elderly medical inpatients with depression, researchers found that at 3 months 18% of patients were well, 43% were depressed and 22%

were deceased. At 12 months or more, 19% were well, 29% were depressed and 53% were deceased. Factors associated with worse outcomes included more severe depression and more serious physical illness. Among those older depressed adults without significant comorbid medical illness or dementia and who are treated optimally, the outcome is more optimistic, with over 80% recovering and remaining well throughout follow-up.[75]

Medical comorbidity, functional impairment and comorbid dementing disorders all adversely influence the outcome of depression.[1] Depression also adversely affects the outcome of the comorbid problems such as cardiovascular disease[5] in which depressive disorder is associated with an increase in mortality,[77] particularly for women and less so for men.[78,79] Problems in meeting one's basic needs affects depression among older adults.[55]

Non-suicide mortality

Psychiatric disorders in general and severe depressive disorders increase the risk of non-suicide-related mortality.[1,5,80] For example, in a review of 61 reports of this relationship from 1997 to 2001, 72% demonstrated a positive association between depression and mortality in elderly people.[81a] Both the severity and duration of depressive symptoms predict mortality in the elderly population in these studies.[1,82] Other studies, however, have suggested that the association between depression and mortality is related to the high correlation between depression and other medical problems. In one study, depression at baseline predicted earlier (3 and 5 year) mortality but not later (10 year) mortality. The interaction between self-rated health and depression independently and strongly predicted mortality at all endpoints,[83] that is, depression impacts non-suicide mortality through intermediate risk factors.

In a recent study,[84] both moderate [multivariate hazard ratio (MHR), 1.29; 95% CI, 1.03–1.61] and severe depression (MHR, 1.34; 95% CI, 1.07–1.68) predicted 10 year mortality after multivariate adjustment. Chronic depression was associated with a 41% higher mortality risk in a 6 year follow-up compared with subjects without depression.

Suicide

The association of depression and suicide across the life cycle has been well established.[85–91] Older adults are at a higher risk for suicide than any other age group. While older Americans comprise ~13% of the US population, they account for 18% of all suicide deaths.[92] Increased risk for suicide attempts in late life is associated with being widow(er)s, living alone, perception of poor health status, poor sleep quality, lack of a confidant and experience of stressful life events, such as financial discord and interpersonal discord.[86,91]

The most common means of committing suicide in the elderly are use of a firearm[88] and drug ingestion.[1] Women attempt suicide more than men; however, men completed suicide more often than women.[93] Although completed suicides increase with age, suicidal behaviours do not increase.[94] This is consistent with the contention that older adults are more intent in their efforts to commit suicide.[95]

There are many risk factors for suicide, with depression being central.[96] Perhaps the best studied factor is pervasive feelings of hopelessness.[97,98] Other psychological constructs include emotional pain,[99] feelings of being a burden and social isolation.[100a] The lack of social networks and their disruption are significantly associated with risk for suicide in later life.[95] Joiner *et al*. have identified key risk factors for individuals at high risk for suicide,[101] and they (as others) have identified 'mattering to others' as an important protective factor.

Physical illness is strongly associated with suicide in the elderly. In one large epidemiological study the following medical illnesses were found to be associated with suicide:[102] congestive heart failure [odds ratio (OR), 1.73; 95% CI, 1.33–2.24], chronic obstructive lung disease (OR, 1.62; 95% CI, 1.37–1.92), seizure disorder (OR, 2.95; 95% CI, 1.89–4.61), urinary incontinence (OR, 2.02; 95% CI, 1.29–3.17), anxiety disorders (OR, 4.65; 95% CI, 4.07–5.32), depression (OR, 6.44; 95% CI, 5.45–7.61), psychotic disorders (OR, 5.09; 95% CI, 3.94–6.59), bipolar disorder (OR, 9.20, 95% CI, 4.38–19.33), moderate pain (OR, 1.91; 95% CI, 1.66–2.20) and severe pain (OR, 7.52; 95% CI, 4.93–11.46). Treatment for multiple illnesses was strongly related to a higher risk and these patients often saw a primary care physician in preceding months before suicidal behaviour, underscoring the physician's potential role in suicide. Indeed, almost half of the patients who committed suicide had visited a physician in the preceding week.

Older persons with mental disorders rarely seek help from mental health professionals, preferring to visit their primary care physician instead.[103] The majority of older adults who die by suicide have been seen recently by a healthcare provider. Suicide prevention strategies rely on the identification of specific, observable risk factors. Depression, hopelessness and self-harming behaviours (such as food refusal) are possible indicators of suicide risk.[95,104] Living alone, feeling like one is a burden to others and having few social ties are each a risk factor for suicide. Individuals with a previous history of suicide are more likely to attempt suicide again.[88] Increased risk is also associated with resolved plans, a sense of courage and/or competence regarding suicide and access to means of suicide (e.g. pills or gun).[105] Other variables that increase suicide risk include substance abuse,[106] marked impulsivity and personality disorder.[107]

Aetiology

Biological

As noted above, increased rates of depression are associated with many medical conditions, including dementing disorders,[57] cardiovascular disease,[81b] hip fractures[108] and Parkinson's disease.[109] Depression has been associated with pain in institutionalized elderly people[110] and is also common among home-bound elders with urinary incontinence.[111] In one study, initial medical burden, self-rated health and subjective social support were significant independent predictors of depression outcome.[112] Therefore, any exploration of the aetiology of late-life depression must begin with the possibility that the depression is caused in part, and perhaps wholly, by physical illness.

The role of heredity, that is, genetic susceptibility, has been of great interest in exploring the origins of depression across the life cycle.[113] Among elderly twins, genetic influences accounted for 16% of the variance in total depression scores on the CES-D and 19% of psychosomatic and somatic complaints. In contrast, genetics contributed minimally to the variance of depressed mood and psychological wellbeing.[114] Attention has been directed to specific genetic markers for late-life depression. For example, a number of studies have focused on the susceptibility gene APOE (the e4 allele) for AD. No association was found in a community sample between APOE e4 allele and depression;[115] however, the APOE e4 allele contributes to AD, which in turn is associated with increased rates of depression. In another study, hyperintensities in deep white matter but not in the periventricular white matter were associated with depressive symptoms, especially in elders carrying the e4 allele.[116]

Much attention has been directed to vascular risk for late-life depression, dating back at least 40 years, although the advent of magnetic resonance imaging (MRI) increased interest considerably.[73,117–120] Vascular lesions in some regions of the brain may contribute to a unique variety of late-life depression. MRI of depressed patients has revealed structural abnormalities in areas related to the cortical–striatal–pallidal–thalamus–cortical pathway,[121] including the frontal lobes,[122] caudate[123] and putamen.[124] These circuits are known to be associated with the development of spontaneous performance strategies demanded by executive tasks. Recent serotonin activity, specifically 5-HT2A receptor binding, decreases dramatically in a variety of brain regions from adolescence through mid life, but the declines slowly from mid life to late life. Receptor loss occurred across widely scattered regions of the brain (anterior cingulated, occipital cortex and hippocampus). Serotonin depletion can also be studied indirectly by the study of radioisotope-labelled or imipramine-binding (TIB) sites. There is a significant decrease in the number of platelet-TIB sites in elderly depressed patients compared with elderly controls and individuals.

In one study, healthy subjects showed a marked increase in cortisol levels 2–3 h into the procedure regardless of drink composition whereas recovered depressed subjects did not. In elderly patients who had recovered from depression, there was no evidence of greater vulnerability of hypothalamic 5-HT pathways to 5-HT depletion. However, they demonstrated reduced reactivity of the HPA axis compared with healthy subjects.[125]

Late-life depression is also associated with endocrine changes. Although the dexamethasone suppression test was long ago ruled out as a diagnostic test for depression, non-suppression of cortisol is associated with late-life depression compared with age-matched controls.[126] Depression is also associated with an increase in corticotrophin-releasing factor (CRF), which mediates sleep and appetite disturbances, reduced libido and psychomotor changes.[127] Ageing is linked to a heightened responsiveness of adrenocorticotropic hormone (ACTH), cortisol and dehydroepiandrosterone sulfate (DHEA-S) to CRF.[128] Low levels of DHEA have been associated with higher rates of depression and a greater number of depressive symptoms in community-dwelling older women.[129] Total testosterone levels have been found to be lower in elderly men with dysthymic disorder than in men without depressive symptoms.[130] However, the efficacy of testosterone in treating depression has not been established.[131]

In addition, Tsai's research suggests that decreased brain-derived neurotrophic factor (BDNF) is related to both AD and major depression.[132] The author suggests that BDNF could be a bridge between AD and depression, explaining both the depressive symptoms in AD and cognitive impairment in depression.

Dementia and depression

The prevalence of depression in dementia is estimated to range between 30 and 50%.[58] Symptoms of depression are common among individuals with dementia, complicating both the diagnosis and treatment, and are often associated with a more severe clinical course, higher cost of treatment, poorer quality of life and worse outcomes. Further, psychiatric symptoms that occur in individuals with dementia are often the primary cause of family burden and distress. Depression in dementia often goes unrecognized, resulting in less effective therapeutic interventions.[133] However, the identification and effective treatment of depressive disorder in individuals with dementia may substantially augment treatment outcome and improve the quality of life for the patient and family.

Depression among individuals with dementia may be more frequent in those with vascular diseases than in

those with AD. Patients with vascular dementia have more frequent and more severe symptoms of depression, and also anxiety, than those with AD (after controlling for levels of cognitive impairment). Ballard *et al*. found that among patients with dementia, 25% had major depression and 27.4% had minor depression.[60] Major depression occurred significantly more often and was significantly more severe in patients with vascular dementia than in patients with AD.

Psychological and social

A variety of different psychological origins have been theorized for depression in later life, including behavioural, cognitive, developmental and psychodynamic theories. Among the behavioural explanations, learned helplessness[134] was originally used to describe the increasingly passive behaviour of dogs who were exposed to inescapable shock. The theory has been expanded, suggesting that one cause of depression is learning that initiating action in an environment that cannot be changed is futile.[134–136] As individuals face new challenges associated with ageing, coping strategies that were once useful may become less effective. Within this context, behavioural interventions (described below) encourage the individual to find new ways to cope successfully with environmental stress.

The most dominant current psychological model of depression is that of cognitive distortions.[137] Several researchers have found consistent differences in the cognitive styles of depressed individuals compared with non-depressed individuals. Beck and co-workers have described the cognitive schema of depressed persons as having logical errors that promote depression.[137–139] Cognitions may be distorted such that the elder has expectations that are not realistic, over-generalizes or over-acts to adverse events and personalizes events. Thus, in reaction to a negative life event (loss of a loved one, move into a nursing home, etc.), an individual's cognitive style may increase the likelihood of a depressive episode.

A developmental theory of ageing, the *disengagement theory* of ageing,[140] contends that there is a mutual social and affective withdrawal between the older adult and their social environment. Similarly, *gerotranscendence*[141] is a concept in which the older individuals are thought to narrow their personal social world and to have a decreased investment in activities that were once important in younger years. Others have conceptualized this withdrawal as a subtype of geriatric depression that has been termed *depletion*.[142] Some have attempted to couple the theory of social disengagement with ageing (much debated in the literature) with depression, suggesting that some symptoms of depression, such as lack of social interest and greater self-involvement, mirror attributes of older adults according to *disengagement theory*.[143,144] Other factors being equal, it is probable that elders who are less socially engaged are more depressed. For example, elders who stopped driving had a greater risk of worsening depressive symptoms.[145] A more recent yet controversial theory complements the depletion theory, suggesting that successful ageing is associated with '*selective optimization with compensation*'.[146] This model is based on the recognition by the elder of the realities of ageing, especially the losses. Such recognition leads to the selection of realistic activities, optimization of those activities and compensation for lost activities, which in turn leads to a reduced and transformed life. More recently, *socioemotional selectivity theory*[147,148] posits that decreasing rates of social contact reflect a greater selectivity in social partners.

Social engagement is a key concept related to depression and the association between late-life depression and impaired social support has been established for many years. Poor social support is strongly associated with depression in the elderly.[149,150] The quality of social support networks has been identified as an important factor in predicting relapse in depressive episodes and future levels of depressive symptoms.[151,152] Further, among the elderly, social support may serve as a buffer against disability,[153] while social disengagement may be a risk factor for cognitive impairment.[154]

Perceived negative interpersonal events are associated with depression among individuals in general and also among elders, particularly in those who demonstrate a high need for approval and reassurance in the context of interpersonal relationships. While social support has been found to be critical in buffering an individual against depression, ironically the interpersonal behaviours of individuals who become depressed are often associated with the withdrawal of social support from friends and family.[155]

Diagnosis

The diagnostic workup of late-life depression derives predominantly from what we know about symptom presentation and aetiology. The diagnosis is made on the basis of a history augmented with a physical examination and supplemented with laboratory studies. Importantly, there is no biological marker or test that creates the diagnosis of depression. However, for some subtypes of depression, such as vascular depression, the presence of subcortical white matter hyperintensities on MRI scanning are critical to confirming the diagnosis.[135,156]

There are several standardized screening measures for depression that are often used by primary care physicians.[157] Examples of such instruments include the Geriatric Depression Scale (GDS) and the Center for Epidemiologic Studies Depression Scale (CES-D).[13,158,159] Screening in primary care is critical. Not only is the

frequency of depression high, but also suicidal ideation can be detected by screening.

Despite the centrality of the clinical interview, other diagnostic tools must be employed to assess the depressed elder. Cognitive status should be assessed with the Mini Mental State Examination (MMSE) or a similar instrument, given the high likelihood of comorbid depression and cognitive dysfunction.[57] Height, weight, history of recent weight loss, laboratory tests for hypoalbuminaemia and cholesterol are markers of nutritional status and are critical given the risk for frailty and failure to thrive in depressed elders, especially the oldest of old.[34,160] General health perceptions and also functional status (ADLs) should be assessed for all depressed elderly patients.[161,162] Assessment of social functioning,[163] medications (many prescribed drugs can precipitate symptoms of depression), mobility and balance, sitting and standing blood pressure, blood screen, urinalysis, chemical screen (e.g. electrolytes, which may signal dehydration) and an electrocardiogram if cardiac disease is present (especially if antidepressant medications are indicated) round out the diagnostic workup.

Differential diagnosis of depression and dementia

Dementia and depression have considerable symptom overlap.[63b] Hence distinguishing between late-life depression and depressive disorders in the elderly is one of the more challenging problems facing healthcare professionals.[164] There are a cluster of cognitive deficits that are common to both dementia and depression. Memory impairment is the most frequent shared symptom.[135,165] In addition, apathy is a common symptom among individuals with dementia, including those with and without comorbid depression, and also among non-demented elderly individuals with depression.[166]

As described elsewhere (Ref, 135, pp. 230–2), clinicians often have difficulty in their attempt to distinguish a primary mood disorder from other problems associated with depressed mood, in particular with what some have referred to as 'pseudodementia' (Ref. 135, pp. 349–72). Pseudodementia is a syndrome in which dementia is mimicked, but the underlying cause is a psychiatric disorder which is typically, but not always, depression.[167]

Memory problems accompanying depression in older age may be present and similar in form to symptoms of dementia. However, depressed elderly patients (without dementia) tend to focus on their memory problems. In contrast, patients with dementia are typically unaware of the extent and severity of their cognitive dysfunction and use strategies to conceal their cognitive dysfunction from others. Wells[167] compared the clinical features of patients with pseudodementia with those with true dementia and found that among the patients who present with depression and cognitive impairment, those who were eventually diagnosed with dementia were more likely to exhibit motivation-related symptoms, such as disinterest, low energy and concentration difficulties.

Treatment

Biological

Evidence-based guidelines for the prevention of new episodes of depression are available, as are care-delivery systems that increase the likelihood of diagnosis and improve the treatment of late-life depression. However, in North America, public insurance covers these services inadequately.[168]

There is clear and mounting evidence for the efficacy of antidepressant medications (both alone and in combination with psychotherapy) in the treatment of older adults with major depression and also for the treatment of dysthymia.[3] Antidepressant medications have become the foundation for the treatment of moderate to severe depression in older adults.[1] Although antidepressant medications are equally effective for treating serious major depression across the life cycle,[169–171] differences in side effects make some antidepressants more desirable. For example, although studies that compare tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) usually find equal efficacy, there are fewer side effects with SSRIs,[172] which make them the first choice for treatment of older adults.[173,174] The antidepressants even appear to be efficacious in subjects with AD and vascular depression.[175,176]

In a recent review of the literature on the effects of antidepressant medications in depressed older adults,[177] it was concluded that the available data, although limited, suggest that the dual-action agents [TCAs and serotonin norepinephrine reuptake inhibitors (SNRIs)] do not appear to confer any additional benefits in efficacy over single-action agents (SSRIs) in the treatment of depression in the elderly.

Interestingly, antidepressants appear less efficacious in treating less severe depression in older adults;[178] similar findings have recently been demonstrated in the general population. The overall evidence suggests that antidepressants and counselling have relatively small benefit in these less severe conditions.[179] However, in a study conducted in a primary care setting, paroxetine (compared with problem-solving therapy) was found to have moderate benefits for depressive symptoms in elderly patients with dysthymia and more severely impaired elderly patients with minor depression.[180] Most of the currently available SSRIs have been demonstrated to be efficacious in elderly people, including fluoxetine (10–20 mg daily),[181] sertraline (50–100 mg daily),[182] paroxetine (10–20 mg daily),[172,183] citalopram (10–20 mg daily)[184] and escitalipram (10–20 mg

daily), whereas duloxetine has not been shown to be specifically efficacious in the elderly population, but studies are ongoing. Other newer-generation antidepressants that have been shown to be efficacious include venlafaxine,[185] mirtazapine[186,187] and buproprion.[188,189]

In a recent consensus of practising geriatric psychiatrists, the SSRIs along with psychotherapy were identified as the treatments of choice for late-life depression, along with venlafaxine. Buproprion and mirtazapine are alternatives [as was electroconvulsive therapy (ECT) in severe depression]. Medication (SSRI plus an antipsychotic, with risperidone and olanzapine being the antipsychotics most commonly recommended) and ECT are the suggested first-line treatments for major depression with psychotic features (yet these patients often must also receive ECT). Psychotherapy in combination with medication is recommended for dysthymic disorder. Education and watchful waiting, in contrast, are recommended for minor depression that lasts for less than 2 weeks (antidepressant medication plus psychotherapy are recommended for minor depression if symptoms persist).

In one consensus report, the preferred antidepressant for treating both major and minor depression is citalopram (20–30 mg) followed by sertraline (50–100 mg) and paroxetine (20–30 mg), with fluoxetine (20 mg) as an alternative. Escitalopram was not on the market when this survey was conducted.[100b]

Nortriptyline (40–100 mg) is the preferred tricyclic agent, with desipramine (50–100 mg) as the alternative. The consensus group recommended continuing the antidepressant for 3–6 weeks before a change in medications is made if the first-choice medication is not effective. If little or no response is observed, the consensus is to switch to venlafaxine (75–200 mg).[1] For a first episode of depression with recovery following antidepressant therapy, 1 year of continual therapy is recommended. For two episodes, 2 years of continual therapy and for three or more episodes, 3 years of continual therapy are recommended.[100b]

The new-generation antidepressants inhibit a number of the cytochrome P450 enzymes that metabolize most medications, such as CYP3A, CYP2D6, DYP2C, CYP1A2 and CYP2E1. The CYP3A enzymes metabolize 60% of the medications used today. Fluoxetine is a moderate inhibitor of CYP3A4. Approximately 8–10% of adults lack the CYP2dD6 enzyme and paroxetine is a potent inhibitor of this enzyme (which may explain, among some patients treated with paroxetine, the lack of efficacy of analgesics such as codeine that are metabolized by this enzyme). Citalopram and venlafaxine are the 'cleanest' of the medications in terms of inhibition of the cytochrome P450 enzymes.[190,191]

Hyponatraemia (39% in one study) poses a clear risk for the elderly on SSRIs or venlafaxine. Frail older adults and those with medical illness should have sodium levels checked before and after commencement of antidepressant medications.[192] The safest practice is to monitor all elders for sodium levels who are on these medications. This hyponatraemia is due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Other serious side effects reported with the SSRIs include the risk of falls (no less risk than with the tricyclics in one study),[193] the serotonin syndrome (lethargy, restlessness, hypertonicity, rhabdomyolysis, renal failure and possible death)[194] and gastrointestinal bleeding.[195] Less serious side effects include weight loss, sexual dysfunction, anticholinergic effects (most pronounced with paroxetine), agitation and difficulty in sleeping.

Psychotic depression in late life responds poorly to antidepressants but well to ECT.[196–199] In one study using bilateral ECT versus pharmacotherapy, the older age group had a better response to ECT than younger age groups.[200] Memory problems remain the major adverse effect from ECT that affects quality of life, but are usually transient and clear within weeks following treatment.

A repetitive transcranial magnetic stimulation (rTMS) could replace ECT in some situations.[201] TMS does not require anaesthesia and seizure induction is avoided. Although not studied specifically in elderly people, in one outcome study patients treated with rTMS compared with ECT responded equally well and their clinical gains lasted at least as long as those with ECT.[202] In another study, executive function improved in both middle-aged and elderly depressed subjects with rTMS compared with sham treatments.[203]

A variety of adjunct physical therapies may alleviate depression. In a community-based study, among subjects who were not depressed at baseline, those who reported a low activity level were at significantly greater risk for depression at follow-up.[204] An aerobic exercise training programme may be considered as an alternative to antidepressants for the treatment of depression in older persons with mild to moderate symptoms.[205] However, the advantages of exercise are not limited to aerobic activities. Unsupervised weight lifting has been found to decrease depressive symptoms up to 20 weeks after induction.[206] Light therapy may also be beneficial, especially if the depression follows a seasonal pattern. Exposure to bright light for 30 min per day improved depression among institutionalized elders in one controlled study.[207]

Psychological

The Prevention of Suicide in Primary Care Elderly Collaborative Trial[208] evaluated the impact of a care management intervention on suicidal ideation and depression in a large sample of older primary care patients. Participants were patients 60 years of age or older with depression identified after screening. The intervention consisted of services of 15 trained care managers, who offered algorithm-based

recommendations to physicians and helped patients with treatment adherence over 24 months. Compared with patients receiving usual care, those receiving the intervention had a higher likelihood of receiving antidepressants and/or psychotherapy (84.9–89% versus 49–62%) and had a 2.2 times greater decline in suicidal ideation over 24 months. Among patients with major depression, a greater number achieved remission in the intervention group than in the usual-care group. Outcomes for those with minor depression were the same regardless of treatment.

Cognitive behavioural therapy (CBT) and interpersonal therapy (IPT) have been shown to be efficacious in the treatment of depression in the elderly, especially in combination with medications. Given that these therapies are short term (12–20 sessions), they are attractive to third-party payers. In addition, the educational (as opposed to a reflective) posture of the therapist employing such therapies is attractive to elders.[1]

CBTs focus on the patient's cognitions surrounding a given negative life event and assist the person to restructure their thought processes cognitively in a more realistic manner. The evidence is clear that treatments aimed at changing cognitive distortions can be fairly effective in decreasing depressive symptoms and even in preventing future relapse. Treatments that focus on problem solving and behavioural activation have also been found to be effective in the treatment of depression. For example, in a study to determine the effectiveness of a home-based programme for treating minor depression or dysthymia among older adults, patients were randomly assigned to an in-home based treatment (Program to Encourage Active, Rewarding Lives for Seniors, PEARLS) or usual care.[5] The PEARLS intervention consisted of problem-solving treatment, social and physical activation and recommendations to patients' physicians regarding antidepressant medications. The intervention was found to reduce depressive symptoms significantly and improve health status in chronically medically ill older adults with minor depression and dysthymia.

Another frequently used treatment for depression is IPT,[209,210] which has been adapted for older adults.[209,211] IPT focuses on four components hypothesized to lead to or maintain depression: grief (e.g. death of a loved one); interpersonal disputes (e.g. conflict with adult children); role transitions (e.g. retirement); and interpersonal deficits (e.g. lack of assertiveness skills). In a study of IPT and elderly depressed patients, clinicians determined that the most common problem areas in therapy were role transition (41%), interpersonal disputes (34.5%) and grief (23%).[212] Miller *et al*. found that IPT was an effective treatment not only with elderly patients with depression but also including those with moderate cognitive impairment.[213]

It is important to note that most studies of depression have found that a combination of psychotherapy and pharmacotherapy has a better outcome than either treatment alone.[214,215]

In a systematic review including 14 randomized controlled trials that assessed the efficacy of psychotherapy for treating depression in elderly people (55 years of age or older),[216] the results of the meta-analysis showed that, compared with a placebo, psychotherapy was more effective in reducing depression (standardized mean difference, – 0.92; 95% CI, – 1.21 to – 0.36). Subgroup analysis showed that cognitive behavioural therapy, reminiscence and general psychotherapy were all more effective than placebo; in contrast to other findings, psychotherapy as an adjunct to antidepressant medication did not increase effectiveness. However, a higher drop-out rate was observed in studies that did not include psychotherapy versus those that did.

The treatment of the elderly depressed has been shown to be cost-effective. In a randomized controlled trial, researchers recruited participants from 18 primary care clinics from eight healthcare organizations in five US States. A total of 1801 patients 60 years of age or older with major depression (17%), dysthymic disorder (30%) or both (53) were randomly assigned to the depression intervention ($n = 906$) or to usual primary care ($n = 895$). Intervention patients were provided access to a depression care manager supervised by a psychiatrist and primary care physician. Depression care managers offered education, support of antidepressant medications prescribed in primary care and problem-solving treatment in primary care (a brief psychotherapy). Relative to usual care, intervention patients experienced 107 (95% CI, 86 to 128) more depression-free days over 24 months. Total outpatient costs were $295 (95% CI, – $525 to $1115) higher during this period. The incremental outpatient cost per depression-free day was $2.76 (95% CI, – $4.95 to $10.47) and incremental outpatient costs per quality-adjusted life-year ranged from $2519 (95% CI, – $4517 to $9554) to $5037 (95% CI, – $9034 to $19 108). The authors concluded that the depression intervention is a high-value investment for older adults; it is associated with high clinical benefits at a low increment in healthcare costs.[217]

Conclusion

Depression has a profound negative impact on older adults, significantly decreasing their quality of life and functioning and increasing both medical morbidity and mortality.[1–5] Although rates of depressive disorders are no greater among the elderly than in the general population, significant rates of depressive symptoms have been identified in elderly populations. Older persons with mental disorders rarely seek help from mental health professionals, preferring to visit their primary care physician instead.[103] Nonetheless, depression among the elderly often goes unrecognized and untreated. However,

when identified and addressed, depression, regardless of age, is a highly treatable illness. There are several psychotherapies that have been specifically developed for the treatment of depression, the most effective being cognitive behavioural therapy and interpersonal therapy. There are antidepressant medications that are efficacious in treating the depressed elderly patient; moreover, a combination of medication and psychotherapy has been shown to produce the most positive outcomes.

Key points

- Depression, the most frequent cause of emotional suffering in later life, is associated with significant losses in health-related quality of life.
- Depression is often comorbid with other disorders, including dementia and medical problems.
- Aetiological determinants of depression include psychological, biological and developmental life-span theories
- There is an association of suicide with depression.
- Depression often goes undetected and untreated; however, when identified it is a highly treatable illness.

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CHAPTER 84

The older patient with Down syndrome

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Introduction

The association between trisomy 21 and Down syndrome was first recognized in 1959 by Lejeune, Gautier and Tarpin. In recent times, the number of fetuses conceived with Down syndrome has increased, but prenatal screening has resulted in a decline in the number of children conceived with this condition. Thus, the occurrence of Down syndrome has decreased from 1 in 700 to 1 in 1000 live births. In addition to the true trisomy, 3–4% of Down patients have translocation of a portion of chromosome 21 and 1% have mosaicism with some cells having 46 and other 47 chromosomes.

From 1983 to 1997, the median age of death of persons with Down syndrome increased from 25 to 49 years.[1] More recently, it was suggested that the average life expectancy for Down syndrome is 60 years.[2] The oldest reported person with Down syndrome lived until 83 years of age. Three factors make persons with Down syndrome of interest to the geriatrician: (1) the increasing life span; (2) the fact that these persons tend to develop early frailty and functional decline in their 40s; and (3) the early onset of Alzheimer's disease.

Genes and Down syndrome

There are 329 genes predicted to be on chromosome 21. Sixteen of these genes play a role in mitochondrial energy metabolism or the generation of free radicals. Abnormalities in these genes are thought to lead to increased free radical production, leading to premature ageing.

At least 10 genes on chromosome 21 play a role in brain development and neuronal loss. Two of these are associated with Alzheimer's disease, namely the amyloid precursor protein and the S100 calcium-binding protein. Overproduction of amyloid precursor protein and, thus, β-amyloid, is thought to play a key role in the early onset of Alzheimer's disease in persons with Down syndrome. In addition, excess production of β-amyloid has been shown to lead to problems with learning and memory, which may contribute to the cognitive problems seen in persons with Down syndrome.

There are six genes that are involved in folate and methyl group metabolism on chromosome 21. Elevated levels of homocysteine, which are seen in folate deficiency, are associated with Alzheimer's disease. In our clinical experience, elevated homocysteine levels are not rare in younger adults with Down syndrome.

The physician, and the patient with Down syndrome

Older persons with Down syndrome are usually easily recognized when they present to the physician, because of the classical facial features (brachycephaly, epicanthal folds and flat nasal bridge) and short stature. These persons also often have broad hands, lax ligaments and a wide gap between the first and second toes, brachydactyly and mental retardation. The majority of persons with Down syndrome live in the community. They may live in group housing and work in sheltered workshops. Physicians need to identify the person who accompanies the individual with Down to the office. This person often provides supervisory care for the individual with Down syndrome and can provide useful historical information on behavioural and other changes that may be occurring. We recommend office visits every 6 months for healthy persons with Down syndrome and every 3–4 months when functional or mental decline is present. This allows the patient to become comfortable with the healthcare provider. Many patients enjoy hugging and this can further increase trust in the physician. However, the physician must remember to ask the patient first if they wish to hug. The physician should always discuss the patient's work and how it is progressing. Also, note should be made of their recreational activities and how they are interacting with other persons within a group home. The quality of life of all patients should be assessed by probing multiple

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areas such as 'things you do, your family and friends, your self-image, your leisure time, your employment and help you need' before exploring the person's health issues.

Always address the person with Down syndrome directly, before hearing the caregiver's story. This gains their confidence and allows observation of their language ability. Finally, never assume that changes in persons with Down syndrome are due to the condition itself before excluding other common medical causes. Problems with spatial memory are classical of Down syndrome and so should not be used in the diagnosis of Alzheimer's disease.[3] Aerobic exercise programmes may help improve both psychosocial and physical health.[4]

For some medical examinations, such as pap smears, and special tests, such as MRI or CT scan, or procedures such as dental care, persons with Down syndrome may require sedation. We have found that 0.5–1 mg of lorazepam orally is usually sufficient for this purpose and produces no adverse effects. Low-dose intravenous lorazepam can also be used in more difficult situations. Others have recommended oral ketamine and midazolam, given under the supervision of an anaesthetist.[5] Before undergoing a procedure requiring sedation, a risk–benefit evaluation should always be undertaken. Informed consent needs to be obtained from the patient or, where applicable, the court-appointed guardian.

Preventive measures for Down syndrome patients should be similar to those for the general adult population. This includes screening for hypertension and heart disease. Because obesity is a common problem in this population, regular counselling on the need for exercise is mandatory. Although, in our experience, most Down syndrome patients do not smoke or drink alcohol, this should be confirmed both from the patient and the caregiver.

Down syndrome adults tend to complain of pain, even when present, less often than other persons. Therefore, it is important to utilize facial expressions during the examination to obtain input concerning presence of pain. Also, such patients may stop using a limb when it is painful. Rocking and 'head banging' behaviours occur as visceral pain proxies. As is the case with older adults, middle-aged adults with Down syndrome often manifest medical problems as a delirium or other behavioural problem.

Persons with Down are a vulnerable population and therefore, like children and older people, are at increased risk for abuse. When adults with Down syndrome become withdrawn, this may suggest abuse or an unrecognized pain syndrome or depression. The presence of unexplained bruises, skin tears or fractures must increase the physician's suspicion of abuse. New-onset falls can suggest delirium, functional deterioration or abuse.

Health counselling includes decisions on advanced directives and guardianship. Financial support questions need to be addressed and relatives need to be aware of local resources. Estate planning, for example trusts, need to be created where appropriate, as Down syndrome persons are now regularly outliving their parents and other close relatives. Parent (caregiver) support groups can be invaluable as caregiver stress is common, particularly as the parent ages. Local and national societies for Down syndrome or for persons with developmental disabilities are an important resource. The physician needs to look for excess stress and/or depression in caregivers and advise treatment where appropriate.

Functional ability using at least basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs) should be assessed yearly. Where possible, mental status screening using the Mini Mental Status Examination (MMSE) or the Saint Louis University Mental Status Examination and the Geriatric Depression Scale or the Cornell Depression Inventory should be done yearly.

There are a number of disease conditions that occur more commonly in adults with Down syndrome than in the general population (Table 84.1). 'Health-Care Guidelines for Individuals with Down Syndrome' were developed by a consensus panel of the Down Syndrome Medical Interest Group.[5] There is a lack of evidence in this area and so physician-substituted judgement is important in deciding

Table 84.1 Conditions that occur commonly in adults with Down syndrome.

Obesity
Periodontal disease
Hearing loss
Visual problems including early cataracts
Aortic valvular disease
– Mitral valve prolapse
– Aortic regurgitation
Arthritis
Hypogonadism (male)
Hypothyroidism
Hyperthyroidism
Diabetes mellitus
Early menopause
Osteoporosis
Coeliac disease
Sleep apnoea
Atlantoaxial subluxation
Testicular cancer
Seizures
Dermatological abnormalities
Depression
Alzheimer's disease
Delirium
Agitated behaviour
Foot problems

which healthcare screening approaches are most efficacious in this population.

Disorders associated with Down syndrome

Endocrinological

Congenital hypothyroidism occurs in one in 141 neonates with Down syndrome and the prevalence increases with age. In adults with Down syndrome, between 15 and 40% have hypothyroidism.[6] Its presentation is often insidious and many of the early signs and symptoms are difficult to detect in patients with Down syndrome. All patients with a recent decline in mental function need to be screened for hypothyroidism. Because of the frequency of hypothyroidism in this population, it is recommended that adult patients are screened by having a thyroid-stimulating hormone (TSH) blood test every year. All patients with a TSH $>10\,\mathrm{mU\,l^{-1}}$ should be treated, regardless of whether or not the thyroxine level is normal. Goitre and thyroiditis also commonly occur in this population. No studies have determined the utility of examining thyroid antibodies to determine which patients will progress to hypothyroidism. Thyroid cancer is extremely rare in this population.

Type 1 diabetes mellitus occurs in over 1% of young persons with Down syndrome. No studies have examined the prevalence of type 2 diabetes mellitus in adults with Down syndrome. However, in view of the high prevalence of obesity, it is generally believed that there is a higher prevalence. Similarly, the metabolic syndrome (insulin resistance, hypertension, hypertriglyceridaemia and hyperuricaemia) is not rare in this group of patients. Uric acid levels are increased in the serum of most patients with Down syndrome.

Male hypogonadism occurs fairly commonly in males in their 40s with Down syndrome. It is predominantly of the secondary hypogonadism type, with low lueinizing hormone and also low testosterone and bioavailable testosterone. Treatment with testosterone can stabilize mood and prevent loss of muscle and bone. Males with trisomy 21 have reduced fertility. Females have a premature menopause of 47.1 years compared with 51 years for the woman without developmental disabilities. At present, based on the findings of the Women's Health Initiative, we are not utilizing estrogen replacement in postmenopausal women with Down syndrome.

Persons with Down syndrome have lower peak bone mass and, therefore, are more likely to develop osteopenia and osteoporosis.[7] This is aggravated by the high use of anticonvulsant medicines in this age-group. Bone mineral density should be measured in all patients with Down syndrome at the age of 50 years. Calcium and vitamin D administration should be initiated at age 40 years for women. All Down syndrome patients should receive 1000 IU of vitamin D daily. The use of hip pads should be considered in Down patients who have frequent falls.

Otolaryngolical conditions

Hearing loss occurs in up to two-thirds of persons with Down syndrome.[8] This can worsen with ageing. In addition, many middle-aged patients have further hearing deterioration because of common impaction. Hearing loss can aggravate speech problems and make the person appear more cognitively impaired than they are or to appear unresponsive to simple requests.

As many as half of the adults with Down syndrome can have sleep apnoea.[9] This is related, in part, to mid-facial hypoplasia and also to their short neck and obesity. While in patients it is of the obstructive type, central sleep apnoea can also occur. Sleep apnoea presents with daytime fatigue and somnolence and night-time snoring with apnoeic periods. Behavioural changes such as irritability or withdrawal can result from sleep apnoea. Diagnosis is made with a sleep study. Some patients will tolerate continuous positive airways pressure, but this is often rejected.

Surgical approaches can help, but the failure rate is relatively high.

Joint problems

Children with Down syndrome can develop a condition similar to juvenile rheumatoid arthritis, associated with subluxation of joints. The diagnosis is often delayed. Similarly, arthritis is often only diagnosed late in adults with Down syndrome.

Atlantoaxial instability occurs in Down syndrome where there is excessive movement of the first cervical vertebra (atlas) on the second one (axis).[10] The diagnosis is made when there is increased space between the posterior segment of the anterior arch of C1 and the anterior segment of the odontoid process. This occurs in 15% of patients with Down syndrome. About 1–2% will have subluxation with neurological signs and symptoms consistent with spinal cord compression (Table 84.2). When this occurs, it is a neurosurgical emergency. However, outcomes of surgery are often poor.

Severe cervical and lumbar-sacral osteoarthritis are fairly common. This is associated with pain, gait disturbance, sometimes hand clumsiness, difficulty in moving and associated behavioural disturbances.

Coeliac disease

Coeliac disease is a malabsorption syndrome that occurs in response to the ingestion of gluten products. It occurs in as many as 7% of Down syndrome patients.[11] It is screened

Table 84.2 Presentation of spinal cord compression in persons with Down syndrome who have atlantoaxial subluxation.

Neck pain
Gait disturbance
Clumsiness of hands
Torticollis
Incontinence
Hyperreflexia
Clonus
Quadriplegia/paresis
Positive Hoffman's and Babinski reflexes

for at 24 months of age. Symptoms include diarrhoea and weight loss. Diagnosis is made by serum antibodies and intestinal biopsy. Coeliac disease can present for the first time later in life and should be considered as the diagnosis in any Down syndrome patients with unexplained weight loss or diarrhoea.

Dermatological conditions

Vitiligo and alopecia are seen in adults with Down syndrome. Dry skin is extremely common and often associated with pruritus. Fungal infections are common and often difficult to eradicate. Seborrheic and atopic dermatitis also occur frequently. A fissured or geographic tongue is present in almost one-third of patients with Down syndrome.

Cardiovascular disorders

Congenital heart disease occurs in about half of the children born with Down syndrome.[12] Some of these, such as isolated secundum atrial septal defects, may have been missed in childhood and present for the first time in adults. Mitral valve prolapse occurs in about half of patients and aortic regurgitation in 17%. In the presence of signs or symptoms, an echocardiogram should be carried out. Alterations in cardiac conduction are not rare and should be considered in those with new onset falls with or without syncope. In those with valvular defects, antibiotic prophylaxis needs to be given before dental care or other instrumentation.

The coronary artery disease death rate is low, possibly because of increased activity of the cystathionine-β-synthase gene, which accelerates the conversion of homocysteine to cysteine, thus reducing homocysteine levels.[13] Persons with Down syndrome are less likely to have hypertension due to a reduction in the expression of the type 1 angiotensin receptor gene.

Dental problems

Gingivitis and periodontal disease are common and lead to tooth loss. Orthodontic problems are common and may not have been able to be corrected during childhood. Bruxism is not rare.

Cancer

In children, both acute lymphoblastic and myeloid leukaemia occur with increased frequency.[14] Whereas most cancers occur with a decreased frequency in persons with Down syndrome,[15] testicular cancers appear to be more common.

Foot problems

These include hallux valgus, hammer toe deformities, plantar fasciitis and early onset of foot arthritis. All of these can result in unstable gait and increased falls. Feet should be examined regularly and the services of a podiatrist utilized when necessary.

Gynaecological problems

Where possible, as in any other adult, Papanicolaou smear and pelvic examination should be carried out. This is often extremely difficult and may need to be deferred. Similarly, mammography should be carried out when feasible. Breast examinations should be done yearly. Early age at menopause is associated with an increase in dementia and earlier mortality in Down patients.[16]

Eye disorders

Refractive errors are present in 40% of adults. Cataracts occur in 3% of patients and keratoconus is present in 15% of patients.

Alzheimer's disease

Alzheimer's disease occurs commonly in Down syndrome patients, starting at the age of 30 years (Table 84.3).[17] Over three-quarters of patients, by the time they reach 70 years of age, may have some symptoms of Alzheimer's disease, although a fairly recent study has suggested that this may be an overestimate.[18] While much of the blame for this has been placed on the trisomy of amyloid precursor protein, recent evidence has suggested that trisomy of DYRK1A leads to hyperphosphorylation of tau protein.[19] The diagnosis of Alzheimer's disease is very difficult to make in persons with Down syndrome. Common early changes are memory loss, loss of conversational skills, withdrawal and functional decline. Decline in executive function is a common early sign of Alzheimer's disease.[20] The diagnosis requires the careful exclusion of other causes of dementia, such as drugs, depression, hypothyroidism, vitamin B_{12} deficiency, visual and auditory problems, space-occupying lesions, for

Table 84.3 Approximate prevalence of Alzheimer's disease in persons with Down syndrome.

Age (years)	Alzheimer's disease (%)
41–50	8.9
51–54	17.7
55–59	32.1
≥60	25.6

example, bilatent subdural haematomas following a fall, or infections. Late presentations associated with Alzheimer's disease include seizures, apathy, focal neurological signs and personality changes.

Epilepsy

Seizures occur in about 8%, with half occurring with the first year of life and half in the third decade or later.[21] We are particularly impressed with the ease of use of keppra, compared with dilantin, in these patients.

Behaviour disorders

Depression occurs commonly. Loss of a parent or caregiver can precipitate depression, as can change in a familiar environment. Problems within the social environment of a group house can also precipitate depression. Most of those who are depressed are treated with selective serotonin reuptake inhibitors. These agents can cause hyponatraemia, leading to delirium.

Aggressive behaviour occurs in about 6% of adults with Down syndrome. Management is difficult. Valproic acid, trazadone, lorazepam and antipsychotics have all been tried but with limited success. Oversedation is often a complication of these treatments.

Delusions of things being stolen from them are common, with a prevalence of 14%. Visual hallucinations tend to be present in the late states of Down syndrome with Alzheimer's disease.[22]

Conclusion

Middle-aged persons with Down syndrome often present with all the special needs of frail older adults. For this reason, geriatricians are the ideal physicians for this group. In addition, some of the special needs of this population make it preferable for them to utilize a physician who cares for a number of patients with Down syndrome. The physician needs to work closely with the interdisciplinary team that provides day-to-day care for these individuals.

Key points

- Down syndrome (trisomy 21) is associated with early onset of frailty and Alzheimer's disease.
- Sleep apnoea occurs commonly in Down syndrome.
- Hypothyroidism, diabetes mellitus, osteoporosis and coeliac disease occur more commonly in Down syndrome patients.
- Subluxation of the cervical spine can lead to spinal cord damage in Down syndrome and is a neurosurgical emergency.

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SECTION 8

Special Senses

CHAPTER 85

Disorders of the eye

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Introduction

The positive association between visual impairment and mortality has been well documented in several longitudinal eye studies[1–7] although the mechanisms for this association are not as well understood.[8,9] Because visual impairment can predict mortality, a better understanding of the common types of visual impairment and their treatments and risk factors should assist practitioners in providing life prolonging medical care.

Five major disorders cause the greatest visual disability: cataracts, diabetic retinopathy, refractive error, macular degeneration and glaucoma. Increasing age is a major risk factor for all five of these disorders. The overall prevalence of refractive error resulting from these five causes of visual impairment is remarkably consistent around the world. Figure 85.1 shows average values for the prevalence of these disorders in people aged 75 and over in the American population gleaned from multiple sources of reviewed literature[10–13] (http://one.aao.org/CE/PracticeGuidelines/PPP.aspx). These numbers were determined from epidemiological studies done in the 1980s. It is reasonable to expect that these percentages may have decreased somewhat with improved treatment options, especially for diabetes mellitus. However, with the increase in persons now over age 75, the number of persons suffering from these visual impairments is still rising.

Visual impairment is often described as a person's most feared disability, and with good reason. In older persons, visual impairment is particularly devastating because it has been associated with dramatic reduction in QOL.[14] As vision declines, people are forced to curtail driving. Those who can no longer see clearly report having a reduction in mobility, and having difficulty walking and leaving their homes to participate in social and religious activities. They report a loss of ability to perform activities of daily living (ADL) such as dressing, shopping and getting in and out of bed safely. Poor vision interferes with the ability to take medications properly. It is also a leading risk factor for falls and fractures which, in turn, are risk factors for placement in both non-institutional and institutional extended care and for loss of independence. In addition, other conditions appear to be strongly comorbid with low vision. These include dementia, depression and delirium and other sensory losses, such as hearing and balance deficits. Thus, vision impairment has profound effects on the older person and it is incumbent upon healthcare providers to identify people at risk for leading causes of visual impairment, and to initiate treatments in a timely manner.

Definitions, treatments, and risk factors

Refractive errors

Refractive error can be described as visual acuity with best lens prescription worse than 20/40. It is the most frequent eye problem and is usually corrected with prescription eyewear. The percentage of people whose visual acuity cannot be improved beyond 20/40 increases dramatically with age: 0.8% for those between 43 and 54 years old, 0.9% for those between 55 and 64, 5% for those between 65 and 74, and 21.1% for those 75 and older. This increasing degree of uncorrected refractive error is due to a number of variables. For example, there is normally an increase in the against-the-rule astigmatism with age and it is often exacerbated during surgery that breaches the conjunctiva such as cataract and glaucoma[15] surgeries. The long-term effects of refractive surgeries such as laser-assisted *in situ* keratomileusis (LASIK) and epi-LASEK that many people are now undergoing for the correction of myopia, hyperopia and presbyopia is being studied.[16] Differences in sample sizes, age and sex distributions, length of follow-up and preoperative spherical equivalents have made it difficult to compare results. More follow-up studies are still needed to distinguish the effect of ethnicity on postoperative visual

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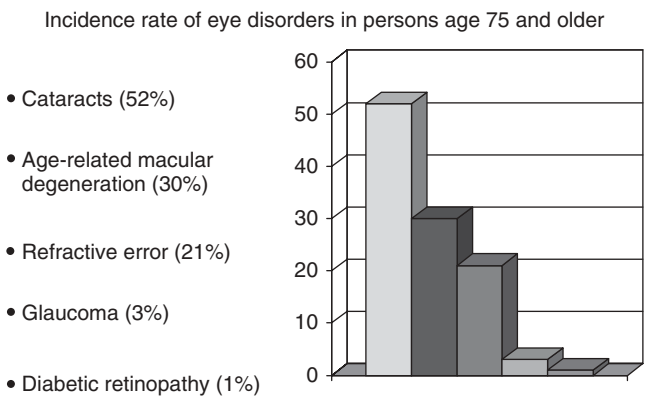

Figure 85.1 Over 50% of Americans aged 75 and older will suffer from visual impairment due to cataracts, 30% will lose central vision from age-related macular degeneration, 21% will have uncorrected refractive errors, 3% will report visual field loss due to optic nerve damage from glaucoma, and 1% will suffer vision loss due to diabetic retinopathy

Table 85.1 Medical risk factors for refractive errors.

- Dry eye
- Cataracts
- Increased glare
- Yellowing of lenses
- Reduction in dark adaptation
- Decreased pupil size (miosis)
- Decreased contrast sensitivity
- Normal hyperopic shift with age
- Increasing against-the-rule astigmatism with age

Table 85.2 Social risk factors for refractive errors.

- Cost of care
- Lack of access to care
- Living in institutional extended care settings
- Lower expectations of patients and providers with age
- Lack of ability to access transportation to receive care

outcomes and standards for reporting surgical outcomes must be set in order to be able to compare efficacy, stability and safety of the different procedures.

The most common refractive error is myopia, or nearsightedness. With this disorder a person has difficulty seeing distant objects clearly. Severe myopia carries with it a large risk of blindness because it is associated with ocular comorbidities such as retinal detachment, macular choroidal degeneration, premature cataract and glaucoma.[17] Genetic studies of myopia have identified several loci that are linked to myopia and a key environmental inverse determinant of myopia is total time spent outdoors.[18] Clearly there is great value in the next decade to performing research on assessing the role of early-age near work versus outdoor activity on genotypes for myopia. This research would provide valuable insight on how to reduce this worldwide epidemic of myopia and its associated high levels of blindness.

There is also a normal hyperopic shift in older adults that may be altered by cataract surgery.[19] Contrast sensitivity decreases with age, in part due to the increased prevalence of dry eye with age, and in part due to the smaller pupil size found in the older person. Dark adaptation also decreases with age and with diseases such as diabetic retinopathy and cancer. Finally, cataracts, yellow lenses and aberrations of the cornea, all of which increase with age, produce glare caused by excess light scattered within the eye. This glare can be debilitating. It can cause difficulty with driving and other tasks conducted in bright light. It can also cause headaches. As people who have been faithful contact lens wearers for decades enter their 70s and 80s, it will be interesting to determine whether the rate of corneal aberrations rises.

There are many risk factors for refractive errors in the older person. Many of the medical and social risk factors are listed in Tables 85.1 and 85.2. Most of these risk factors can be handled with annual dilated fundus eye exams and instructions to seek medical treatment at the first sign of worsening vision. For many persons, that translates into instructions to seek vision care when they notice that they are having more difficulty with their every-day activities due to vision changes.

Age-related macular degeneration

Age-related macular degeneration (AMD) is a disorder of the macula characterized by the presence of drusen, hypo- or hyper-pigmentation of the retinal pigment epithelium (RPE), local atrophy of the RPE and choriocapillaris, neovascularization of the macula, and a reduction or loss of central vision.[12] AMD is the leading cause of severe, irreversible vision impairment in developed countries. Ninety percent of the AMD cases are of the non-exudative (dry or atrophic) type. Ten percent are of the exudative (or wet) type. Non-exudative AMD is characterized by the presence of drusen and loss of RPE and photoreceptors. Sight in the central visual field is lost gradually. Exudative AMD is characterized by a much more rapid loss of central vision due to neovascularization of the choroid and its accompanying haemorrhages that lead to retinal and RPE detachments and scarring. Although non-exudative AMD is more prevalent, most of the people with severe vision loss have exudative AMD.

The National Eye Institute (2010) lists the risk factors for developing AMD as age over 60, obesity, Caucasian race, smoking, family history, being female[20] (although

estrogen has not been implicated in increased AMD risk)[21] and exposure to sunlight.[22] Currently, there are no pharmaceutical treatments for AMD. However, patients with dry AMD should receive regular dilated fundus eye exams and should be encouraged to increase their consumption of antioxidants. They should be educated about how to use an Amsler grid to screen for the progression of dry AMD into wet AMD and encouraged to seek medical attention at the first sign of new symptoms. Dietary consumption of fresh fruits and vegetables is encouraged because they contain antioxidants such as Vitamin C, Vitamin E, carotenoids, selenium and zinc, which are thought to neutralize damage caused by free radicals. Those who have unilateral AMD should be encouraged to take supplements in order to reduce their chances of developing AMD in the other eye. Results from the National Eye Institute Age-related Eye Disease Study (AREDS) showed that supplements containing high levels of antioxidants and zinc significantly reduce the risk of advanced AMD and its associated vision loss.[23] (As an aside, it should be noted that the same nutrients had no significant effect on the development or progression of cataract.) If the patient requests it, advice on developing a diet to help maintain a healthy weight and increase consumption of antioxidants should be provided in written form.

Routine examinations for patients with wet AMD should include optical coherence tomography (OCT) in order to monitor changes in retinal thickness due to both the presence of drusen in the retinal pigment epithelium and blood caused by retinal bleeding. OCT allows the structural integrity of the retina to be followed during therapy. In an effort to preserve residual vision, retinal bleeding is currently controlled by laser photocoagulation but this is not a curative therapy.

There are several ongoing research studies on surgical treatments for wet AMD that is no longer responsive to diet and supplements. Wet, or neovascular, AMD is a complex disease. Several studies have looked at the role of angiogenic agents that probably contribute to choroidal neovascularization.[24–27] To date, no clear treatment guidelines have been developed for the anti-angiogenic therapies.

Although there are several environmental risk factors for AMD, the future of some treatments may indeed be rooted in the genome. To that end, researchers are looking at genotypic variation for AMD. Although AMD is a complex disease, about 40% of the genetic variance can be explained by variations in five common single-nucleotide polymorphisms (SNPs).[28] Other SNPs have been associated with risks for common treatments such as photodynamic therapy or bevacizumab treatment.[29] Recent advances in these inexpensive genetic technologies may allow medicine to produce personalized diagnosis and treatment plans for AMD.[30]

Finally, persons with advanced AMD may be classified as legally blind and often require assistance with ADLs even if the AMD is monocular because contrast sensitivity is affected, thereby reducing visual acuity in the unaffected eye. They are also at significant risk for depression. Vision can often be enhanced by the use of low vision aids such as magnifiers and bright lights. Motivated patients can be taught to read with the peripheral retina. Because functional status and QOL are related, every effort should be made to encourage patients to seek rehabilitation.

Risk factors for, and other factors associated with, AMD are listed in Tables 85.3 and 85.4.

Diabetic retinopathy

Diabetic retinopathy (DR) is a leading cause of blindness in the industrialized world in people between the ages of 25 and 74,[31] and the fourth leading cause of blindness in people of all ages in developing countries.[32] Annually, between 12 000 and 24 000 diabetic patients in the United States become legally blind as a result of complications of diabetic retinopathy.[33] Every diabetic patient is at risk for several changes to vision that occur as a result of uncontrolled systemic diabetes mellitus (DM) of long duration, including numerous ocular and periocular changes that characterize diabetic retinopathy. DR is a disorder of the retinal vasculature. Resulting changes are characterized by waxy exudates, micro-aneurysms, punctate haemorrhages and, less frequently, neovascularization, all of which lead to a decrease in visual acuity and, perhaps, to blindness. Indeed, the elderly diabetic patient is 1.5 times more likely to develop vision loss and blindness than is an age-matched non-diabetic person.[34]

DR can occur with both type 1 (insulin deficient) and type 2 (non-insulin dependent) diabetes mellitus. Despite

Table 85.3 Confirmed risk factors for AMD.

- Smoking
- Female sex
- Advanced age
- Caucasian race
- Low levels of antioxidants
- Exposure to sunlight in early adulthood

Table 85.4 Factors associated with AMD.

- High-fat diet
- Alcohol use
- Hormonal status
- Family history of AMD
- High levels of C-reactive protein
- High intake of saturated fats and cholesterol

the fact that type 1 diabetics develop the disease at an earlier age, a greater number of type 2 diabetics will develop DR because more than 90% of diabetics have type 2 diabetes. DR progresses from its mild, non-proliferative stage with increased vascular permeability, to severe, non-proliferative DR which is characterized by vascular closure, to proliferative DR with neovascularization in the retina and on the vitreous humour which tends to produce vitreal haemorrhages and resultant vision loss, retinal detachment and possibly, glaucoma. Vision loss can result in several ways: (1) central vision can be lost due to macular oedema or capillary loss; (2) neovascularization can lead to retinal detachment; (3) pre-retinal or vitreal haemorrhages can obstruct vision; (4) glaucoma can result in response to the damage caused by DR.

The retinal damage caused by DR cannot be cured. However, DR does respond favourably to early detection and treatment of diabetes and to case management of the disease.[35] Annual dilated fundus examinations are recommended for early detection and management of DR. Laser photocoagulation significantly reduces vision loss.[36] Finally, for those who have experienced vision loss, low-vision care and rehabilitation is recommended. These recommendations on how to minimize vision loss associated with DR are particularly significant in light of the research that shows that vision loss contributes significantly to poorer health, more disability and increased frequency of falls in diabetics[37] as well as restrictions in reading, mobility, work and leisure activities.[38]

Diabetics are at greater risk for comorbid conditions. The presence of diabetes mellitus increases the risk for the development of cataracts. In turn, the presence of cataracts complicates both the patient's and the provider's abilities to monitor vision changes due to DR. In addition, diabetics are at greater risks for complications during cataract surgery. Finally, comorbid conditions such as hypertension and hyperglycaemia can worsen DR and should be treated.[39] Risk factors of and other factors associated with diabetic retinopathy are listed in Tables 85.5 and 85.6.

Management and treatment of DR is multifold. It should include dietician-monitored diets that are individualized to the patient's diagnosis and treatment goals, taking into account eating habits and other lifestyle factors. A supervised exercise programme helps with glycaemic and blood pressure control which, in turn, delays both the onset and progression of DR. Currently, laser photocoagulation and vitrectomy remain the conventional management protocols for DR.[13] Many new studies on the treatment of DR have been initiated based on the observations that microvascular damage to patients with chronic hyperglycaemia is mediated by interrelated pathways involving aldose reductase, advanced glycation end products, protein kinase C (PKC) and vascular endothelial growth factor (VEGF). Many new pharmacological agents are currently being tested for their abilities to slow or reverse the progression of DR. However, the recent publication of results from a randomized, controlled study that compared the efficacy of photocoagulation versus intravitreal injection of triamcinolone acetonide indicates that although the triamcinolone acetonide appears to reduce the risk of progression of DR, it also causes adverse events such as cataract formation and glaucoma.[40] Preliminary data on the role of human erythropoietin (EPO), a primary regulator of erythropoiesis, in the pathophysiology of DR[41] indicates that researchers are continuing to search for pharmaceutical solutions to the progression of DR.

Table 85.5 Risk factors for diabetic retinopathy.

- Duration of diabetes
- Late diagnosis of diabetes
- No perception of vision problems
- Lack of frequent evaluation of vision
- Uncontrolled or poorly controlled blood sugar level (HbA1c)
- Presence of other systemic diseases such as hypertension and hyperglycaemia

Table 85.6 Factors associated with diabetic retinopathy.

- Age
- Race
- Obesity
- Smoking
- Clotting factors
- Renal disease
- Use of angiotensin-converting enzyme inhibitors

Glaucoma

Glaucoma is a general term that refers to a number of disorders of the optic nerve that are often accompanied by increased intra-ocular pressure (IOP) (ocular hypertension) and that results in a gradual and progressive visual field loss when the optic nerve is damaged. Glaucoma is the second leading cause of legal blindness in the United States and the leading cause of legal blindness in African-Americans.[42] The destruction of the optic nerve that occurs as glaucoma progresses causes gradual loss of peripheral vision. As the disease progresses, the field of vision gradually narrows and blindness can result. Glaucoma has no early symptoms so about half of the people who are affected are unaware they have the disease. By the time people experience problems with their vision, they usually have a significant amount of optic nerve damage.

Early detection of glaucoma is critical. If glaucoma can be controlled, serious vision loss can be prevented. Comprehensive dilated eye examinations are recommended at least

once every two years for African-Americans over age 40 and all people over age 60. Primary open-angle glaucoma (POAG) is the most common form of glaucoma and one of the nation's leading causes of vision loss. POAG has a characteristic loss of retinal ganglion cells and atrophy of the optic nerve that occurs in the presence of an open and normal looking angle. The visual field loss may be monocular but if it is binocular, it may well be asymmetric[13] (http://www.aao.org/aao/CE/PracticeGuidelines/PPP.aspx).

Currently, there are no primary prevention strategies for glaucoma. Therefore, it is important to optimize early detection by understanding the risk factors for glaucoma.[42,43] These factors are listed in Table 85.7. The only modifiable risk factor is elevated baseline IOP. Perhaps in the next edition of this book more research will have been done on the effects of modifiable socioeconomic characteristics such as nutrition, exercise, smoking, sleep apnoea and body mass index (BMI).

Treatment to control IOP is helpful in reducing the visual field losses associated with glaucoma, regardless of whether the patient has elevated or normal (low-tension) glaucoma.[14] Drug therapy, in the form of eye drops, is normally initiated to reduce the production and/or increase drainage of aqueous humour. These drops may be beta-blockers, alpha-agonists, carbonic anhydrase inhibitors (CAIs), prostaglandin-like compounds, cholinergic agents, or epinephrine compounds. If these eye drops fail, CAI pills may be prescribed. This large choice of treatment agents hints at the variability found in the types of glaucoma. Research studies are just beginning to show us the genetic variability of glaucoma.[44–46] The efficacy of a drug has been shown to be affected by the genetic make-up of the recipient.[47,48] This concept that generic variation contributes to a person's response to therapy is both a boon and a bane. Personalized medicine is fast becoming the Holy Grail of effective medicine but the cost of that success will include the need for practitioners to become savvy about health legislation, discrimination, employment issues, insurance regulations and ethics, as well as medicine.[49] Surgery is recommended once a patient becomes intolerant of the drugs, is not compliant with the drug schedule, or is unresponsive to the drug. Trabeculoplasty is a form of laser surgery that opens clogged trabecular meshwork, thereby allowing aqueous humour to drain out of the anterior chamber more rapidly.

Table 85.7 Risk factors for glaucoma.

- Age greater than 60
- Central corneal thickness
- Elevated intraocular pressure
- African descent over age of 40
- Family history (parent or sibling)

Trabeculoplasty does not always give a permanent solution so eye drops are often continued or reinstated over time. When both the eye drops and the trabeculoplasty are no longer effective, a filtering procedure called trabeculectomy is done. This procedure cauterizes a part of the trabecular meshwork. For patients with secondary glaucoma or for children with glaucoma drainage implants are used to drain aqueous humour.

The efficacy of surgical interventions, the number of times each of the surgeries needs to be repeated, and the order in which the surgery types are offered in combination, differ for black and white patients.[50] Further study will undoubtedly fine-tune future surgical interventions.

Before determining whether the disease will be treated with eyedrops or surgery, an effort must be made to determine the patient's health status and life expectancy, how difficult daily treatment of eyedrops will be, how expensive the drug costs are, and what the possible side effects will be.

The use of marijuana as a complementary therapy for POAG glaucoma is not recommended. NEI studies have demonstrated that some derivatives of marijuana do result in lowering IOP for 3 to 4 hours when administered orally, intravenously, or by smoking. However, potentially serious side effects included increased heart rate, a decrease in blood pressure, impaired memory of recent events and impaired motor coordination.

Efforts to better understand the pathogenesis of glaucoma have led to attempts to locate gene anomalies associated with glaucoma. Defects in the *myocilin* gene (MYOC) have been associated with POAG and defects in PITX2, FOXC1 and CYP1B 1 are associated with anterior segment development.[51] The risk factors for and other factors associated with glaucoma are summarized in Tables 85.7 and 85.8.

Cataracts

Cataracts are a leading cause of blindness worldwide.[11] They are opacities of the lens or the lens capsule. Cataracts are *named* by the location of the opacity; the opacity may occur in the nucleus (nuclear cataract), in the lens cortex (cortical cataract), or in the lens periphery (coronary

Table 85.8 Other factors associated with glaucoma.

- Late onset menarche
- Migraine headaches
- Peripheral vasospasm
- Low diastolic perfusion pressure
- Presence of AMD, hypertension or diabetes
- High ratio of *n*-3 to *n*-6 polyunsaturated fat
- Suspicious optic nerve appearance (cup-to-disc ratio greater than 0.5)

cataract), or posterior (posterior subcapsular, posterior cortical and posterior polar cataracts).

Cataracts are caused by the hardening of the lens that occurs as a part of normal ageing. They also may occur as a result of blunt trauma, but the history of this type of cataract is a rapid onset and a rapid rate of progression. Normal cataracts progress slowly and may be present for years before they are noticed.

Cataracts are not normally life-threatening. No effective medical treatment for cataract exists, but a diet rich in lutein and zeaxanthin, carotene and Vitamin A, and long-term Vitamin C supplementation are thought to slow the progression of cataracts.

Once the patient reports a decreased QOL or impaired function, elective surgery can correct the visual impairment. For patients with glaucoma, AMD, or diabetes, where visualization of the fundus is necessary for continuing management and treatment, surgery may be indicated before the patient reports a decline in functional status.[12,13,52]

When vision becomes cloudy enough to bother the patient, surgery can remove the clouded lens and replace it with an IOL implant. Surgery is normally an outpatient procedure using local anaesthetic. Phacoemulsification (ultrasonic cataract removal) is used to emulsify the lens for easy removal (although promising research on the use of lasers to break up the lens is ongoing).[53] An IOL is then implanted within the empty lens capsule to serve as the new lens. Normally the incision is self-sealing. The surgical procedure is so safe that it has changed little in the past 10 years although lens implants of differing powers can reduce dependence upon glasses for either reading or distance work.

Table 85.9 General risk factors for all cataracts.

- Age
- Diabetes
- Cost of treatment
- Low socioeconomic status
- Diet low in lutein and zeaxanthin
- Lack of education about cataracts

Table 85.10 Risk factors specific for cortical cataracts.

- Iris colour
- Hypertension
- Hyperglycaemia
- Family history
- Abdominal obesity
- Low body mass index
- Exposure to UV-B radiation

Table 85.11 Risk factors specific for nuclear cataracts.

- Smoking
- Iris colour
- Family history
- Low education level
- Non-professional occupation
- Occupational sun exposure in third decade of life

Table 85.12 Risk factors specific for posterior subcapsular cataracts.

- Smoking
- Hyperglycaemia
- Inhaled corticosteroid use
- Systemic corticosteroid use
- Alcohol consumption
- Exposure to UV-B radiation

Many risk factors have been associated with cataracts although the studies have been largely observational. General risk factors for cataracts are listed in Table 85.9 and specific risk factors for cortical, nuclear and posterior subcapsular cataracts are listed in Tables 85.10–85.12.

Summary

Each type of eye disorder discussed above has unique risk factors, ranging from diet to environment. Increased age is associated with all of the eye disorders, that is, the frequency of the disorder in the population increases with age. In addition, some of the risk factors are shared by two of the eye disorders. Excessive exposure to sunlight is a risk factor for both cataracts and macular degeneration. Additionally, a particular symptom may have more than one cause. For example, glare may be caused by corneal aberrations or by the development of cataracts. A decrease in contrast sensitivity may be the result of decreased illumination to the retina because of a decreased pupil size, but it may also be caused by AMD, glaucoma, or diabetic retinopathy. A decrease in dark adaptation may be caused by a miotic pupil or it may also be caused by cataracts. Thus, treatment of a specific visual deficit may require more than one approach because due consideration must be given to how different disorders contribute to the resulting morbidity.

In addition to having shared risk factors, there is some degree of comorbidity between the eye disorders. Either cataracts or glaucoma may often co-occur with DR, and AMD often co-occurs with glaucoma. Interactions between diseases may complicate the treatments needed to prevent visual impairment and blindness. Finally, although there is little research about how comorbid eye disorders affect

an already decreased level of function and QOL, the QOL of patients is dependent upon better understanding of the interactions between diseases and between their treatments.

For people who become blind from an eye disorder, there is some hope. Research on artificial vision techniques is ongoing. Artificial vision through the use of cortical implants is a promise of the future,[54] although it is designed to promote mobility, not reading. These cortical implants are contraindicated for people with severe chronic infections and for those blinded by stroke or cortical trauma. However, cortical models for patients without viable optic nerves (e.g. glaucoma patients) and retinal prostheses for those without viable photoreceptors (e.g. AMD patients) are under development. Research such as this should considerably brighten the future of visually impaired people.

Key points

- Increasing age is a risk factor for loss of vision due to the following eye disorders: cataract, age-related macular degeneration, refractive error, glaucoma and diabetic retinopathy.
- Poor vision due to refractive error and cataracts is often reversible.
- Loss of vision due to diabetic retinopathy, glaucoma and age-related macular degeneration is not recoverable.
- Vision impairment caused by these eye disorders has a negative impact on functional status, mobility, independence and cognitive status of elders.
- Education and visual rehabilitation play important roles in improving the quality of life of persons with visual impairments.

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CHAPTER 86

The ageing auditory system – pathology and epidemiology of age-related hearing loss

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Age-related hearing loss (ARHL), improperly assimilated into presbycusis, is one of the most prevalent chronic conditions in elderly and its social impact is progressively increasing with the global ageing of the population. This particular handicap has traditionally been underestimated, since in many people's minds, hearing deterioration with ageing is a normal evolution. However, accidents related to hearing loss are not uncommon and inability to communicate generates frustration and isolation that can contribute to depressive syndromes or cognitive impairment. Prevention of these adverse consequences is necessary and possible through rehabilitative measures, which have been shown to improve quality of life. Improvement of screening and rehabilitation should therefore become a public health priority. The first part of this chapter is dedicated to the auditory system, its disorders and their diagnosis. The second objective is to provide an overview of hearing impairment epidemiology in the elderly population, based upon large cross-sectional and longitudinal studies and to consider the management of hearing loss in the elderly population.

The auditory system

Physiology of hearing

Sound

Sound is an aerial variation of pressure, producing an acoustic vibration. It is characterized by its frequency – measured in hertz (Hz)–perceived as the *pitch*, and its pressure – measured in decibels (dB)–perceived as the *loudness*.

A normal human ear perceives a pitch between 20 (low pitch) and 20 000 Hz (high pitch).and is able to perceive loudness from 0 to 120 dB. Sounds louder than 120 dB elicit a painful sensation. The scale of loudness is logarithmic, providing the human ear with a very wide dynamic range (Table 86.1). Further, the sensitivity of the ear is better for frequencies around 1000 Hz, covering the voice frequencies range.

The human ear

The human ear is divided into three segments

1 The external ear is composed of the external auditory meatus and the pinna. Its role is to gather the environmental sounds, to amplify them in the 2–5 kHz range and to drive them to the eardrum. It protects the delicate middle ear structures from external trauma.

2 The middle ear is composed of the tympanic membrane (eardrum), the ossicular chain (malleus, uncus, stapes) and the middle ear cavities (tympanic cavity, mastoid, Eustachian tube). It transforms the acoustic energy of sound into mechanical movement transmitted to the inner ear. It protects the inner ear from external (atmospheric) or endogenous pressure variations.

3 The inner ear includes the auditory organ, called the cochlea, and the balance organ. The cochlea is embedded in a solid bone structure, the otic capsule, which contains liquids (perilymphatic and endolymphatic fluids) and the sensory hearing organ, called the organ of Corti. Vibrations of the stapes through the oval window impulse a fluid circulation into the three ramps, that stimulate hair cells contained in the organ of Corti. Hair cells are organized according to the sound frequency, that is, tonotopically, in a spiral shape. The base of the cochlea responds to high-frequency sounds and the apex responds to low-frequency sounds. Inner hair cells represent the transducer, that is, the sensory cells, whereas outer hair cells are devoted to frequency selectivity, improving speech intelligibility.

Auditory pathways

Inner hair cells synapse with a rich array of dendrite that converge to the spiral ganglion, from where the auditory

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 86.1 Dynamic scale of sound pressure level.

Pressure (dB)	Hearing sensation	Communication type	Noise type
130	Protection necessary		
120		No possible discrimination	
110	Painful		Airplane during take-off
90	Painful	No possible conversation	Car horn at 4 m
80		Conversation possible but difficult	Noisy traffic
70	Loud but bearable	Loud voice	Normal traffic
60	Common noise	Conversation with background noise	Supermarket
50	Moderate noise	Quiet conversation	Office
30	Quiet	Whispered voice	Quiet room
20	Very quiet		Sound of a mild wind
10	Unusual silence		Double-walled soundproof room
0	Normal hearing threshold		

nerve starts. The auditory nerve crosses the cerebellopontine angle to the cochlear nucleus, inside the brainstem. Afterwards, auditory fibres are divided in bilateral folds; the main auditory pathway crosses the middle line to the opposite side and reaches the temporal lobe to the primary auditory area. From this primary auditory area, different networks of neurons go towards secondary auditory and cognitive areas, integrating a multisensorial network.

Assessment of hearing function

Subjective measurements

The Rinne test and Weber test are common *tuning fork tests* that can help in differentiating conductive from sensorineural deafness. In the Rinne test, the tuning fork is placed on the mastoid and the skull transmits the sound to the cochlea until the subject's hearing threshold. The tuning fork is then placed next to the external auditory canal, the perception of the sound indicating a normal conductive mechanism. In cases of conductive deafness, the sound is perceived louder by bone conduction than by air conduction. In the Weber test, the tuning fork is placed centrally on the skull. Under normal conditions, the sound is transmitted to both ears equally. In the presence of conductive deafness, the sound is lateralized in the affected ear because the middle ear acts as a resonating drum. In sensorineural deafness, lateralization is observed in the healthy ear as the cochlea does not perceive transmitted sound.

Table 86.2 Degree of hearing loss according to the average hearing loss.

Mild	From 21 to 40 dB
Moderate	From 41 to 70 dB
Severe	From 71 to 90 dB
Profound	From 91 to 110 dB
Total (= deafness)	Above 110 dB

Pure-tone audiometry measures the subjective hearing threshold in various pure-tone frequencies for air conduction (through headphones) and for bone conduction (through a vibrator). The results are presented graphically and the average hearing loss is calculated by averaging hearing thresholds into 500, 1000, 2000 and 4000 Hz. Based on the average hearing loss, hearing impairment can be categorized from mild to total (Table 86.2). Under normal conditions, air conduction is similar to bone conduction. In the presence of conductive deafness, air conduction is at least 15 dB poorer than bone conduction. In sensorineural hearing loss, both air and bone conduction are affected. Mixed hearing loss is a combination of air and bone hearing loss.

Speech audiometry yields a better evaluation of the subject's functional status. This examination is usually performed using headphones and the subject is asked to repeat words from a standardized list, at various intensities. The percentage of correct answers is reported graphically according to the corresponding intensity. The speech reception threshold is the intensity for which 50% of words are correctly repeated. The optimal discrimination score is the highest score that can be achieved. Under normal conditions, it is obtained using a loudness level about 30 dB above the pure-tone threshold. Pure-tone audiometry and speech audiometry are the main evaluation criteria in the assessment of a rehabilitative measure (surgery or hearing aid), before and after intervention.

Suprasegmental tests are not used in current clinical practice. Speech perception in noise (SPIN) evaluates central auditory function.[1] Stereoaudiometry is useful for evaluating the impact of unilateral hearing loss. Gap detection and decay tests are used to diagnose auditory neuropathies.

Questionnaires and screening tests for hearing impairment are recommended by several national institutions for public health, but no standardized procedure has been shown to improve long-term hearing outcomes. However, routine screening would certainly be helpful since the psychosocial impact of hearing loss is significant and effective rehabilitative measures for hearing impairment are available. There are many simple tests for hearing that have been used as

Table 86.3 Hearing Handicap Inventory for the Elderly – Screening.

		Yes	Sometimes	No
E1	Does a hearing problem cause you to feel embarrassed when you meet new people?	4	2	0
E2	Does a hearing problem cause you to feel frustrated when talking to a member of your family?	4	2	0
S1	Do you have difficulty hearing when someone speaks in a whisper?	4	2	0
E3	Do you feel handicapped by a hearing problem?	4	2	0
S2	Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbours?	4	2	0
S3	Does a hearing problem cause you to attend religious services less often than you would like?	4	2	0
E4	Does a hearing problem cause you to have arguments with family members?	4	2	0
S4	Does a hearing problem cause you difficulty when listening to the TV or radio?	4	2	0
E5	Do you feel that any difficulty with your hearing limits or hampers your personal or social life?	4	2	0
S5	Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?	4	2	0
Totals for each column				
Grand total (add all Totals above) [a]				

[a]If the grand total score is greater than 10, an audiological evaluation is recommended.
Adapted from Ventry and Weinstein.[2]

Box 86.1

The minimum assessment in case of hearing loss should include an otoscopy, a pure-tone audiometry and a speech audiometry.

part of the physical examination, such as the whispered voice test. The degree of hearing loss is related to the furthest distance at which patients correctly discriminate words that have been whispered. This method may be used as a screening test but its reproducibility appears erratic. Screening hearing loss with a vibrating tuning fork has also been evaluated, but again, this method provides insufficient objective and reproducible outcomes.

The same self-administered questionnaire, the Hearing Handicap Inventory for the Elderly – Screening (HHIE-S), has been used in several cross-sectional studies and showed significant value in screening for hearing impairment[2] (Table 86.3). This instrument is a 10-item, 5 min questionnaire that measures the degree of social and emotional handicap due to hearing loss. The patient respond 'yes' (4 points), 'sometimes' (2 points) or 'no' (0 points) to each question concerning a particular handicap (Box 86.1). The total score ranges from 0 (no handicap) to 40 (maximum handicap). A total score of 0–8 indicates a 13% probability of hearing impairment, a score of 10–24 indicates a 50% probability of hearing impairment and a score of 26–40 indicates an 84% probability of a hearing impairment.[3] Scores of 10 and above provide a sensitivity between 63 and 80%[4] and a specificity between 69 and 77%. These levels seem acceptable since HHIE-S measures a functional but not audiometric hearing loss.

The Glasgow Benefit Inventory (GBI) is a measure of patient benefit developed especially for otorhinolaryngological interventions. Patient benefit is the change in health status resulting from this intervention. The GBI was developed to be maximally sensitive to ORL interventions, such as hearings aids, middle ear surgery or cochlear implantation. The change in quality of life is categorized between 'much worse' and 'much better' in three domains, physical, social and general, and is reported as a score ranging from −100 to +100.[5]

The Abbreviated Profile of Hearing Aid Benefit (APHAB) is a 24-item assessment inventory in which patients report the amount of trouble they experience with communication or noises in various everyday situations. Benefit is calculated by comparing the patients' reported difficulty in the unaided condition with their amount of difficulty when using amplification. The APHAB produces scores for four subscales: ease of communication, reverberation, background noise and aversiveness.[6]

The audioscope represents another screening instrument that can be used and is recommended by the Canadian Task Force on Preventive Health Care. It is a hand-held combination of an otoscope and an audiometer that delivers a pure tone from 25 to 40 dB at frequencies of 0,5, 1, 2 and 4 kHz. The audioscope is positioned directly in the external auditory canal with a probe tip sealing the canal. Tones are presented at each frequency and the listener's threshold is determined according to his/her responses. The probe is also used for direct inspection of the ear canal and the tympanic membrane. Patients with abnormal otoscopy and/or elevated hearing thresholds may then be referred for specialized evaluation. The sensitivity of audioscope testing exceeds 90%[4,7] and its specificity is estimated to be between 69 and 80%.

Objective measurements

Tympanometry is a measure of acoustic admittance, which depends on tympanic membrane integrity or stiffness, or the presence of a middle ear effusion. Thus, tympanometry is an additional tool in the diagnosis of the cause in

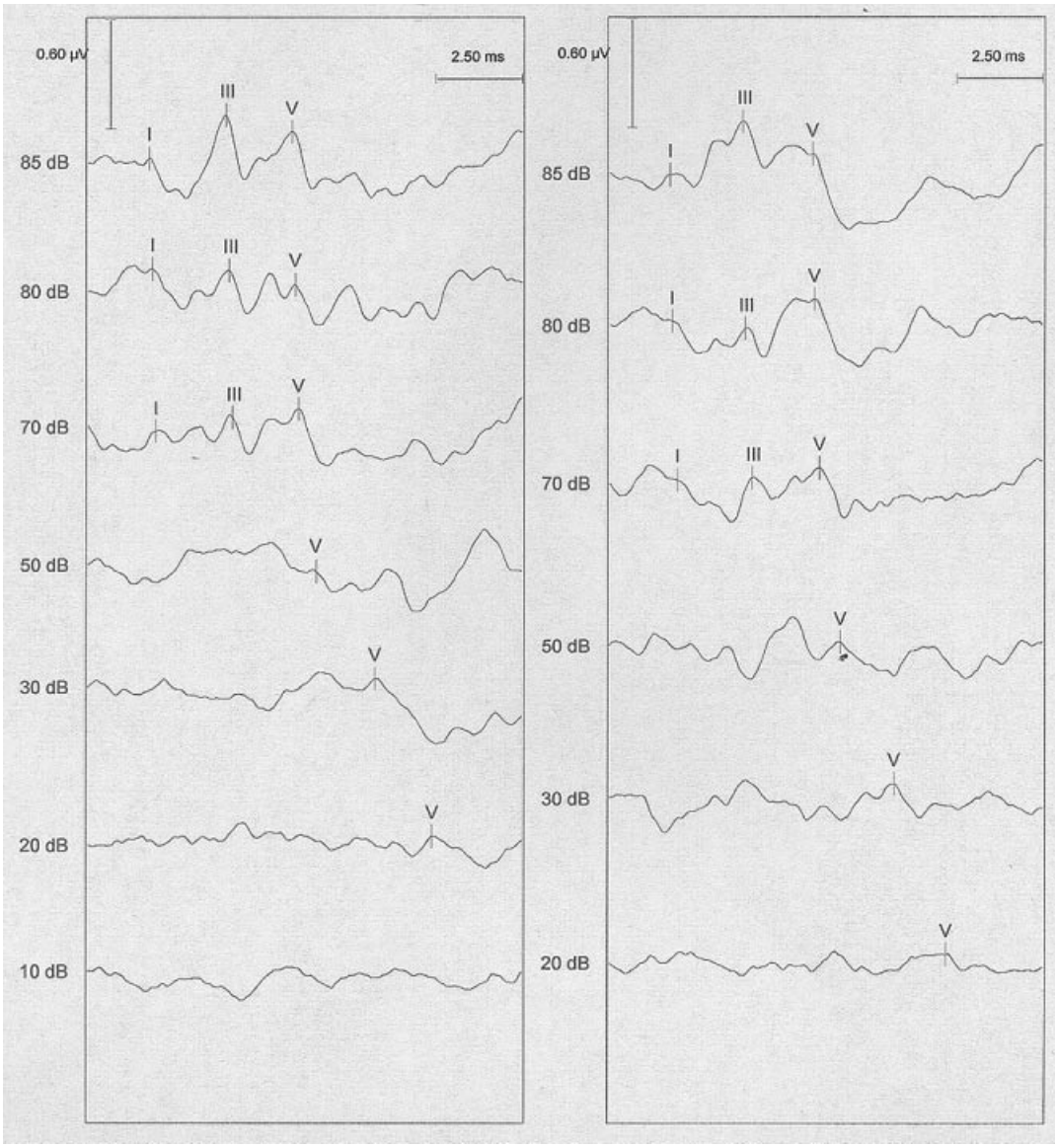

Figure 86.1 Auditory brainstem responses (right ear and left ear). Wave I, distal portion of cochlear nerve; wave II, proximal portion of cochlear nerve; wave III, cochlear nucleus; wave IV, superior olivary complex, nucleus of lateral lemniscus; wave V, inferior colliculus.

some cases of conductive deafness. It is also used to assess functioning of the muscle of the stapes, which reflects the integrity of the ossicular chain and of the facial and the cochleovestibular nerves.

Auditory evoked brainstem responses (Figure 86.1) are an electrophysiological examination that provides an objective assessment of auditory pathways function, from the external ear to the brainstem. Analysis of latency and delay between the recorded waves provides an objective threshold of hearing above 2 kHz and helps in localization of hearing loss cause (external or middle ear, inner ear, nerve lesion).

Evoked otoacoustic emissions are an acoustic response that is produced by the outer hair cells in the cochlea and which bounces back out of the cochlea in response to a sound stimulus. The test is performed by placing a probe that contains a microphone and a speaker into the external auditory canal. The sound stimulus is generated in the probe and, while the sound is processed by the cochlea, a second and separate sound is emitted by outer hair cells and comes back into the external auditory canal. This response is recorded and represented graphically.

Imaging may be used as an additional tool in the aetiological diagnosis or in the preoperative assessment.

High-resolution computed tomographic (CT) scanning provides an accurate representation of the mastoid, the middle ear cavities and the otic capsule that contains the cochlea and vestibular end organs. In chronic otitis media, it may

specify a cholesteatoma extension and more particularly to the facial nerve, to the tegmen tympani or to the inner ear. It confirms otosclerosis, showing a hypodensity of the otic capsule, anterior to the oval window.

Magnetic resonance imaging (MRI) is mandatory in cases of asymmetric sensorineural hearing loss to rule out a cerebellopontine angle tumour and ventricular system dilatation. A vestibular schwannoma appears as a tumour enhanced after gadolinium injection during T1 sequence. MRI is also performed in the cochlear implant preoperative assessment to confirm the presence of auditory nerve and labyrinthine fluids.

fMRI and PET scanning are still research investigations and not used currently for isolated hearing disorders.

Pathology

The ageing auditory system

External and middle ear

With age, external ear skin shows various changes in its physical properties, such as atrophy, dehydration and decrease in elasticity. Combined with reduced self-cleaning abilities of the external auditory meatus and increase in cerumen (wax) production, older adults have a tendency to impact cerumen. Elderly people fitted with hearing aids are more exposed to this cerumen impaction. Further, they may experience dermatitis due to intolerance to hard materials.[8]

The tympanic membrane becomes thinner and its vascularization decreases. Arthritic changes can affect ossicle joints. Atrophy and degeneration progressively affect middle ear muscles and ligaments. Nevertheless, the changing conditions of the middle ear with age do not affect hearing significantly and inner ear changes with age account for most age-related hearing losses.

Inner ear

Biological ageing of the inner ear has been studied through many reports concerning temporal bones histopathology. Schucknecht has been one of the most active contributors to anatomical and histological studies of presbycusis.[9] He described six distinct categories of presbycusis according to their histopathological features: sensory, neural, strial, cochlear conductive, mixed and intermediate presbycusis. In sensory presbycusis, histology shows typically a loss of sensory hair cells that first occurs at the extreme basal end of the cochlea (high-frequencies region) and a degeneration of supporting cells, such as Deiters and Hensen cells. Noise exposure might play an important role in this type of age-related hearing loss as it usually affects outer hair cells. Age-related neural hearing loss is characterized by a loss of spiral ganglion cells and a discrepancy between speech and pure-tone audiometry, speech discrimination being poorer than pure-tone audiometry thresholds would lead one to expect. Histopathology of age-related strial hearing loss involves a loss of strial tissue and strial cells, resulting in an atrophy of stria vascularis, primarily in the apical and middle turns of the cochlea. Strial atrophy might be the most prominent histological finding in age-related hearing loss[10] and affects all frequency regions. Age-related mixed hearing loss represents an association of two or more inner ear histological changes and age-related intermediates characterized by submicroscopic alterations to intracellular organelles in hair and supportive cells. Cochlear conductive hearing loss is due to loss of elasticity of the basilar membrane and/or diminished attachment of the spiral ligament.

Auditory pathways and auditory brain

In addition to biological ageing of neurons, the decrease in peripheral input from ears may lead to a central auditory hearing loss that account for specific auditory deficiencies, such as temporal resolution and binaural processing. Age-related changes in the auditory brain are neither well documented nor specific. Neuronal alterations with age are characterized by shrinkage of neuronal stromas, which tend to accumulate lipofuscin more than in younger neurons and a reduced volume of central structures. Changes in sensory input resulting from age-related peripheral auditory pathology induce a functional and possibly structural reorganization of auditory brain. For instance, the central frequency map (i.e. central tonotopy) may be modified in the brainstem (inferior colliculus) and in the auditory cortex, by occurrence of a progressive high-frequency hearing loss, that leads to an over-representation of neurons responding to lower frequencies.[11] Connections between auditory cortices and higher levels areas, such as language processing sites, might also be altered secondarily to attenuation of auditory peripheral input.[12]

Types of hearing loss (HL)

Recent advances in the knowledge of HL suggest a modern classification of hearing impairment, as described by Zeng and Djallilian.[13]

Conductive HL

Conductive HL usually involves abnormalities of the external and/or the middle ear, due to mechanical or inflammatory causes, accessible to physical examination.

Cerumen accumulation is the most frequent cause of conductive HL; deafness occurs when the occlusion of the ear canal is complete or the cerumen impinges against the tympanic membrane.

In *acute otitis media*, hypoacusia appears behind pain and hyperthermia.

Chronic otitis media can impair hearing through different mechanisms: a perforation in the tympanic membrane, a lysis of the ossicular chain, a fixation of the ossicular chain by tympanosclerosis or a reduced vibration due to

middle ear effusion. Several forms of chronic otitis media must be distinguished. Middle ear effusion and tympanic membrane perforations are the more benign conditions. Retraction pocket is an evolutive chronic otitis media due to a dysfunction of gas exchange in the middle ear. The retraction pocket is potentially dangerous; it progressively erodes the incus and the stapes and extends to the different cavities of the middle ear. Its ultimate evolution stage is the cholesteatoma, which is an abnormal and growing mass of keratin debris. Cholesteatoma has a lytic potential and can destroy ossicles, tegmen tympani or the inner ear. Therefore, cholesteatoma can lead to severe complications such as total deafness, vertigo, mastoiditis, facial nerve palsies, lateral sinus thrombosis, meningitis or temporal abscesses. As it is painless, its evolution is insidious in elderly persons. The diagnosis of chronic otitis media is based on HL associated with chronic or intermittent otorrhoea.

Otosclerosis is the most common cause of conductive deafness with normal tympanic membrane. Although it is known to occur in younger persons, aged patients may also be concerned, especially if otosclerosis worsens a concomitant presbycusis. It is characterized by a fixation of the stapes due to a focal osteodystrophy.

Cochlear HL

The most common cause of cochlear hearing loss in elderly is presbycusis. Typically, this deafness is characterized by a bilateral, symmetrical and progressive high-frequencies hearing loss. An early symptom is speech discrimination impairment in background noise or several speakers' conversations, which makes communication challenging in most social settings. The highest frequencies (6–10 kHz) are initially affected but once the loss progresses to the 2–4 kHz range, discrimination of consonants can be affected with frequent confusion of phonemes that requires repetition of utterances.

Idiopathic unilateral sudden hearing loss is not uncommon. Several pathophysiological factors have been proposed but the aetiology is not yet clear. Viral infections, immune disorders and microvascular injuries have been implicated but the viral hypothesis seems to be the most robust.[14]

Neural HL

Neural HL is also called 'auditory neuropathy' or 'auditory dyssynchrony'. It is due to dysfunctional synapse between inner hair cells or to lesions of the auditory nerve itself. The cochlear function is normal. The most significant characteristic is a temporal processing deficit, leading to a speech perception difficulty whereas the degree of HL is low.

Unilateral sensorineural deafness can appear suddenly or progressively. In both cases, complementary explorations (auditory brainstem responses associated with vestibular caloric testing and/or MRI) must be performed to search for a vestibular schwannoma, a benign tumour affecting the cochleovestibular nerve and developing in the cerebellopontine angle.

Central HL

Hearing impairment due to central lesions is usually defined as a central auditory processing disorder. Cochlear and nerve functions are considered normal. This type of HL is often associated with language impairment, learning disability and attention deficits. Although it is essentially observed in children, it may be associated with cognitive disabilities in the elderly population.

Epidemiology of hearing

Prevalence of hearing disorders in the elderly

In the next 10 years, the number of individuals over the age of 65 years is set to outnumber those under the age of 5 years for the first time in history and by 2040, those over 65 years old will make up 14% of the total world population.[15] Public health policies have to be reshaped regarding new needs that will emerge from this demographic shift. Hearing impairment requires considerable attention because the prevalence of age-related hearing loss (i.e. presbycusis) is increasing dramatically. At the same time, as old adults live healthier and longer, their lifestyle is changing and most of them experience an active retirement. Communication skills are therefore expected to remain normal or near-normal even if natural evolution of presbycusis is worsening hearing.

According to the Royal National Institute for Deaf People,[16] there are already 300 million people in the world with presbycusis and by 2050 it is projected that there will be 900 million. Prevalence studies of hearing impairment in the elderly find varying results according to the age range considered and the definition of hearing impairment that is used. Hence there may be a potential discrepancy between audiometric hearing thresholds and self-reported hearing impairment, due to under- or overestimation of the hearing handicap. The study of the Framingham cohort,[14] consisting of 1475 patients over a 6 year period, established that hearing loss is the third most prevalent condition in older Americans after hypertension and arthritis; between 25 and 40% of the population aged 65 years or older is hearing impaired. This prevalence increases with age, ranging from 40 to 66% in patients older than 75 years and more than 80% in patients older than 85 years. Hearing deterioration appears different according to the frequency that is considered. For instance, in the same study, hearing threshold worsening was more important in high frequencies (between 10 and 15 dB at 8 kHz over 6 years) than in low frequencies (between 1 and 8 dB at 250 kHz). The right ear advantage, that is, better thresholds

in the right ear for pure-tone audiometry and speech perception, that exists in young normal hearing subjects tends to increase with ageing. In the UK, presbycusis is estimated to affect 40% of people aged 61–80 years in its mild form (hearing loss >25 dB) and a further 20% if the hearing loss is >35 dB.[17] A recent UK Health Technology Assessment report[18] revealed lower but still significant proportions regarding the range for age: 12% of people aged between 55 and 74 years have hearing problems and 14% present a hearing loss exceeding 35 dB on pure-tone audiometry. Even though the results differ slightly from one study to another, all of them highlight the growing number of hearing-impaired people and the effect of age on the prevalence of presbycusis.

Risk factors

Age-related hearing loss (ARHL) is the result of interaction between physiological degeneration and environmental factors, medical disorders and associated treatments and individual susceptibility.

Non-genetic risk factors (Box 86.2)

Noise exposure is the best documented risk factor for HL. The primary lesion is the loss of outer hair cells. At this stage, speech intelligibility is altered, whereas pure tone audiometry may be preserved. Noise exposure has a cumulative effect: duration of exposure and natural degeneration of the inner hair cells due to age will increase the sensorial deficit.[19]

The effect of smoking has been proved to be a strong risk factor for HL. Based on a meta-analysis, Nomura *et al*.[20] suggested that minimizing exposure to smoking maintains healthy hearing acuity and smoking cessation may be a cost-effective strategy in a hearing health programme.

Alcohol abuse and repetition of head traumas have also been implicated.[21] Arterial hypertension[22] and more particularly elevated systolic blood pressure is a recognized risk factor for hearing loss, whose detection and treatment are common in a general practice. Thus, several studies have shown that stroke, myocardial infarction, high body mass index and diabetes mellitus were all associated with excessive hearing loss.[10] Maintenance of a healthy general status would then prevent hearing worsening.

Box 86.2

The main non-genetic risk factors for age-related hearing loss are arterial hypertension, noise exposure and ototoxic drugs. They should be treated or prevented. Associated conditions such as cognitive impairment or depressive symptoms should also be investigated.

Table 86.4 Ototoxic drugs.

Antibiotics	Aminoglycosides, erythromycin, vancomycin, streptomycin
Antineoplastics	Cisplatin, carboplatin, vincristine sulfate
Loop diuretics	Furosemide, ethacrynic acid
Anti-inflammatory	Salicylates, quinine

Special attention must be paid to the medication in the ageing population and the iatrogenic potential also exists in otology, since a considerable amount of drugs can have ototoxic side effects (Table 86.4) The ototoxic effects of aminoglycosides and platinum compounds are well documented but one should also assess the risk of using high doses of aspirin or furosemide.

Genetic factors

Familial history is not uncommon in ARHL. According to Gates *et al*.,[23] heritability estimates indicate that 35–55% of the variance of ARHL is attributable to the effects of genes. The study of the Framingham cohort[24] shows that heritability would especially interfere in strial age-related hearing loss, where all frequencies are affected (flat audiogram). Genetic inheritance of ARHL should be distinguished from genetic HL, which is diagnosed from infancy to adult age and is now well documented. In contrast, most of the candidate genes for presbycusis are still under investigation.[25] As genome-wide association studies are expensive and time consuming, most current genetic linkage researchers use genotyping of pooled samples or target candidate genes in large populations of hearing-impaired elders. To date, GRHL2,[26] a transcription factor in a variety of epithelial tissues that is expressed in cells of the cochlear duct, and GRM7,[27] a metabotropic glutamate receptor expressed in inner ear hair cells and spiral ganglions, have shown a significant association with ARHL. Further, some genetic mutations have been shown to interact with environmental factors and enhance the risk of HL. For instance, the 1555G mitochondrial DNA mutation sensitizes the inner ear to aminoglycoside antibiotics.[28]

Associated pathologies and influence of hearing on behaviour

Poor hearing has been identified as a significant risk factor for mortality in elderly people, via increased disability for walking and cognitive impairment,[29] and its coexistence with several medical conditions is now well documented. Hearing impairment favours isolation and dependence in socioenvironmental interactions, which may negatively influence self-esteem and relationships with others. A recent review of the literature concerning risk factors for depression in the elderly[30] highlighted the role of sensory degeneration and more particularly hearing loss.

In patients with hearing loss, the mean odds ratio (OR) for depression across reviewed studies was 1.71 [95% confidence interval (CI), 1.28–2.27]. In another study of 580 patients over 65 years of age, Saito *et al*.[31] compared one group of hearing-impaired subjects with a group of normal hearing subjects. Incidence of depressive symptoms was 19.4% in the first group versus 8% in the group without a hearing handicap; the OR for depression was 2.45 (95% CI, 1.26–4.77). This strong association between hearing loss and depression emphasizes the altered quality of life in hearing-impaired elderly persons.

Quality of life measurements are necessary because they reflect the burden that represents hearing handicap in a patient's daily life and because they may estimate effects of rehabilitative measures. Furthermore, quality of life studies may assist in the allocation of public resources, such as finance and delivery of healthcare services. As previously mentioned, the effects of hearing impairment may be measured based on generic questionnaires or scores more specific to hearing, such as the HHIE-S. A correlation between hearing impairment (determined using HHIE-S scores) and independence for daily life activities (measured via the Katz index) was found to be significant in a study by López-Torres Hidalgo *et al*.[32] which emphasized the influence of hearing status on autonomy. A study of 2431 subjects aged >48 years by Chia *et al*.[33] evaluated the relationship between hearing thresholds and generic quality of life indices from the 36-item Short Form Health Survey. In this study, half of all participants reported hearing problems and the rate of hearing-impaired individuals increased from 16% in 50–59-year-olds to 65% in 70–79-year-olds. The authors found an adverse association between hearing thresholds and social or emotional dimensions of the questionnaire. For example, hearing impairment negatively impacted on emotional withdrawal, intimate relationships and family distress. Effects of hearing impairment on the physical dimension were also found, although this probably reflected a more general decline that can occur with ageing. Activities such as walking or preparing meals were found to be difficult by hearing-impaired elders. They then evaluated the use of hearing aids and its effects on quality of life measurements. Among people with hearing impairment, 33.3% owned a hearing aid and only 25.5% used it habitually, with physical scores that tended to be better than for subjects not using their hearing aid.

Cognitive status and relationship with hearing loss

As mentioned previously, elderly persons must deal with global ageing of hearing structures, from the external ear to auditory cortex, and a global decline of the auditory system is probably a current condition. More than a co-occurrence, peripheral hearing loss and cognitive decline interact and enhance the hearing handicap. Thus, oral communication relies not only on normal auditory structures and pathways, but also on basic cognitive processes. For instance, attention facilitates speech reception and the listening working memory provides a mental system for storage and processing of information: the elderly have to recognize incoming words and to integrate them with just previously heard words in order to give a meaning to the discourse to which they are listening. If the listener has to focus his/her mental energy to perform the first operation due to hearing impairment,[34] processing of speech by the listening working memory may be disrupted, with limited speech comprehension as consequence.

Interactions between hearing impairment and cognitive status exist but their nature is still under investigation. Poor auditory thresholds are common in patients with cognitive decline, and a higher prevalence of hearing loss in populations of adults with a diagnosis of dementia than in comparable population free of such a diagnosis is regularly shown.[35] However, the reasons underlying this association remain unclear and under discussion: a primary central auditory processing disorder due to Alzheimer's temporal lesions is a valuable hypothesis, but the psychosocial consequences of hearing loss just emphasized are recognized risk factors for dementia. Further, hearing impairment may interfere as a bias in neuropsychological assessments of patients. In a study of 82 elderly persons categorized into three groups according to their clinical dementia rating scale scores, central auditory testing using a dichotic sentences discrimination test revealed a strong deficit in patients with mild cognitive impairment or Alzheimer's disease, whereas peripheral testing using pure-tone audiometry and auditory brainstem responses did not show a difference between groups.[36] On the other hand, Acar *et al*.,[37] in a study of 34 hearing-impaired patients, showed an improvement of scores in the Mini Mental State Examination after 3 months of peripheral rehabilitation via hearing aids, associated with significant positive changes regarding daily life and social activities.

In summary, hearing and cognitive functions are closely related and interdependent. To specify the characteristics of this relation, future studies will have to confront results of central auditory processing tests, audiometric tests and validated neuropsychological measures in patients with various degrees of cognitive impairment.

Tinnitus

Tinnitus is a conscious perception of a sound in the absence of an acoustic stimulus. Objective and subjective tinnitus must be differentiated (Table 86.5). Patients with objective tinnitus are hearing real sounds, whether pulsatile or clicking, which are normally inaudible. Usually, pulsatile tinnitus is related to turbulent blood flow that reaches

Table 86.5 Aetiology of tinnitus.

Type	Cause
Subjective	
Otological	Noise-induced hearing loss, presbycusis, sudden deafness, labyrinthitis, otitis media, otosclerosis, impacted cerumen
Neurological	Head trauma, multiple sclerosis, vestibular schwannoma
Drug-related	Salicylates, loop diuretics, platinum-derived, aminoglycosides
Objective	
Pulsatile	Vascular tumours (glomus), arteriovenous malformations, carotid stenosis, severe hypertension, high cardiac output (anaemia)
Muscular	Palatal myoclonus, temporo-mandibular joint dysfunction, spasm of stapedius or tensor tympani muscle

the vicinity of the cochlea and clicking sounds are linked with an abnormal muscular contraction in the middle ear. Pulsatile tinnitus should alert the practitioner to use a stethoscope on the head, looking for an arteriovenous malformation or a glomus jugular tumour.

The pathophysiology of subjective tinnitus remains unclear, but cochlear damage seems to be the cause in most cases. The cochlear injury leads to reorganization of central auditory pathways, as evidenced by neuroimaging studies that have shown hyperactivation of auditory cortices and the limbic system in patients with tinnitus. Tinnitus may be characterized by different features: lasting, lateralization, loudness, pitch. Transient tinnitus, typically after exposure to a loud sound, is a common experience, but many people, and especially those over 65 years old, suffer from a continuous or repetitive tinnitus. Physical examination of the external ear and the tympanic membrane eliminates obvious causes of tinnitus and/or hearing loss, such as cerumen impaction or otitis media. The impact of tinnitus on hearing function must be evaluated with pure-tone audiometry and speech audiometry. As unilateral hearing loss, persistent unilateral tinnitus necessitates the search for a retro-cochlear pathology as a vestibular schwannoma. Quality of life questionnaires, such as the Tinnitus Questionnaire, allow the effects of tinnitus on sleep, emotional status and social activities to be quantified.

Management of ARHL

Medical and surgical treatments

Family and personal otological priors can help in the aetiological investigation of the deafness. The physical examination includes a complete cardiovascular and neurological systems examination. Otoscopy is the main step in the diagnosis of external or middle ear abnormalities causing conductive deafness and the practitioner should keep in mind that cerumen accumulation is a trivial but common cause of hearing loss (up to 30% in the elderly).

Conductive hearing loss

Cerumen impaction can be revealed by simple physical inspection of the external auditory canal. Small hooks and curettes can be used to remove cerumen, and ear canal irrigation with warm water can be applied. Hydrogen peroxide-containing solutions may be used to loosen firm cerumen accumulation. In cases of tympanic membrane perforation or prior ear surgery, the patient can be referred to an otolaryngologist for safe removal or microsuction under microscopic examination.

Middle ear effusion can be diagnosed by otoscopy. The inspection of the tympanic membrane reveals the presence of serous fluid (i.e. serous otitis) or seromucuous secretions behind the membrane. There is no evidence of any medication efficiency but steroid inhalers are commonly used. In cases where effusion persist for several weeks, patients should be referred to an otolaryngologist for surgical treatment (transtympanic tube) and a complete ENT examination, as nasopharyngeal carcinoma may be revealed by a unilateral serous otitis.

Other chronic otitis media must be referred for a complete audiological and anatomical evaluation. The otolaryngologist may propose surgical treatment in cases of cholesteatoma or tympanic membrane perforation with iterative infections. In contrast, they may propose a regular follow-up for a retraction pocket without any auditory or infective consequences.

Otosclerosis also requires treatment by a hearing specialist. Surgical treatment (stapedotomy or stapedectomy) or rehabilitation with a hearing aid may be considered.

Sensorineural hearing loss

Patients with unilateral hearing loss must be referred to an otolaryngologist for a complete assessment of the hearing loss and an aetiological investigation (including a specific search for a vestibular schwannoma). Sudden hearing loss is a controversial topic in many respects. We have already discussed the various pathogenic factors that have been implicated and studied. Conflicting reports concerning the treatment approach have also generated uncertainty. So far, systemic glucocorticoids are the only treatment whose efficiency has been demonstrated in a placebo-controlled trial.[38] Additional use of antiviral agents or hyperbaric oxygenation has been proposed but no evidence for its efficacy has been provided. Most recent studies have assessed the use of transtympanic drug delivery, with particular interest in local administration of steroids.

Prevention plays an important role in hearing impairment care. For instance, hearing must be regularly evaluated when known ototoxic agents need to be administered. Early detection of a high-frequencies hearing loss may help to adapt drugs and doses in order to prevent a secondary deterioration. The use of earplugs provides a 15–25 dB attenuation of sounds and can prevent noise-induced hearing loss. Screening and treatment of systemic cofactors, such as arterial hypertension or smoking, would logically reduce the risk of hearing loss.

The environment may be adapted to the hearing disability through simple measures (turning off the television or radio during a conversation, speaking more slowly) or with the use of an assistive hearing device (telephone amplifier, infrared system for television). Most of these systems may be tested and prescribed in audiology services. For patients wearing hearing aids, frequency-modulated systems, consisting of a microphone placed near the source of sound, a transmitter and a receiver worn by the patient can be used in difficult hearing conditions.

Acoustic amplification via a hearing aid is indicated when the average hearing threshold reach 40 dB on the pure-tone audiogram and can be proposed for smaller losses according to the professional or occupational needs. There are various types of hearing aids, according to the size and shape, including the traditional behind-the-ear, in-the-ear and open-fit models. The audiologist plays a major role in the selection and fitting of the hearing aid, adapted to the patient. Many factors, such as severity of deafness, anatomical configuration of the external ear, social conditions and fine motor skills must be considered. Analogue hearing aids are usually less expensive than digital ones, but the latest provide multiple programmes that operate adaptively and can reduce a noisy background or acoustic feedback. Improvement of quality of life has been shown for a long time in patients wearing hearing aids. Mulrow *et al*.[39] conducted a randomized clinical trial comparing 95 deaf patients fitted with hearing aids with 99 patients without a hearing aid. The first group showed significant improvements in social life, emotional status and cognitive functions whereas these parameters had not been modified in the second group. The size and shape of hearing aids may influence satisfaction. In various studies,[40,41] the in-the-ear type has been identified as the easiest to manipulate and the most often used (45.4 versus 19.5 h per week for the behind-the-ear type). In both studies, patients with a behind-the-ear hearing aid reported significantly more 'undesirable' experiences (ear discomfort, negative sound experience), but the emergence of open fit behind-the-ear aids has significantly decreased these manifestations.

Unfortunately, it is estimated that only 3–20% of potential hearing aid users actually purchase them and most elderly persons are reluctant to do so because of hearing aids' social standing.[41] Moreover, only 60–75% of people will continue wearing their hearing aid once they have been fitted with it.[42] The reasons for dissatisfaction or non-use are cosmetic, unconsciousness of hearing disability, intolerance to amplification and local trauma.

Tinnitus

Patients with tinnitus should be referred to the otolaryngologist for several conditions:

- tinnitus associated with a hearing loss and/or an abnormal ear condition
- persistent (>3 months) unilateral tinnitus
- persistent intrusive tinnitus
- pulsatile tinnitus unless associated with acute otitis media.

The impact of tinnitus on quality of life can be major and associated depressive symptoms must be taken into account. Unfortunately, medical treatment of tinnitus is challenging and the doctor–patient relationship is strongly involved. Many drugs (benzodiazepines, tricyclics, peripheral vasoactives) have been tested but no evidence for their efficacy has been found. As in drug-induced hearing loss, ototoxic medication must be known and eventually adapted in cases of tinnitus. For instance, salicylates can provoke only temporary tinnitus and hearing loss[43] if the cessation is early enough.

Masking devices cover up the tinnitus and provide relief for some patients who have a response to masking during the audiological evaluation. Hearing aids may be proposed if there is an associated hearing loss and some programmes implement masking sounds in the frequency range where tinnitus is most prominent.

Auditory implants

Middle ear implants and bone-anchored hearing aids (BAHAs)

Some elderly people cannot wear hearing aids for medical (chronic external otitis, external auditory canal stenosis) or cosmetic reasons and present a hearing loss that is not severe enough to match cochlear implantation criteria. They may be good candidates for active middle ear implants that may be used to treat mild to severe sensorineural, conductive or mixed hearing losses. A middle ear implant requires a surgical intervention and consists of an audio processor that encodes acoustic signals to mechanical vibrations of a transducer positioned against an element of the ossicular chain. BAHAs require a simpler surgery under local anaesthesia and it relies on bone conduction of sound vibration. Outcomes of middle ear implants in the elderly population as a subgroup have not been specifically documented but most studies report an audiometric gain and

an improvement of speech comprehension in quiet or in challenging conditions.[44] Middle ear implants would be particularly indicated in elderly persons who experience difficulty in manipulating hearing aid controls or suffer from recurrent inflammation of the external auditory canal due to the hearing aid.

Box 86.3

Patients with age-related hearing loss may benefit from several rehabilitative measures, medical and surgical treatments, from hearing aids to cochlear implants, including speech therapy and environmental adaptations.

Cochlear implants

Audiometric criteria for implantation have been progressively extended from total to severe hearing loss.

Cochlear implants are established as effective in elderly patients but there is a justified reticence to operate owing the fragile condition of many elderly patients. Actually, intra- or postoperative complication rates remain comparable to those in younger patients[45] and improvement in speech recognition scores has such a positive impact on quality of life that cochlear implantation has become a robust alternative in rehabilitation of severe to profound deafness.[46] Vermeire *et al*.[47] compared audiometric results and quality of life changes for three age groups (<55, 56–69 and 70+ years). Even though the oldest group had poorer speech recognition scores than the two younger groups, all groups experienced significant improvement of speech recognition and all had similar quality of life outcomes (Glasgow Benefit Inventory, Hearing Handicap Inventory for Adults). Shin *et al*.[48] studied gains after implantation in conversation with familiar or unfamiliar persons and in perception of environmental sounds in a group of elderly implanted patients compared with a control group of younger patients. The results between the two groups were comparable in all conditions. For instance, the gain in conversation with a familiar person was 59% in the elder group versus 58% in the younger group. Further, many patients retain residual hearing in at least one ear and are advised to use the cochlear implant in one side and their hearing aid in the contralateral ear (i.e. bimodal stimulation), if the latter still transmits acoustic information although not providing sufficient speech discrimination. The combination of residual hearing and cochlear implant has been widely evaluated and seems to improve auditory gain and comfort in challenging listening conditions (background noise, reverberant places, music perception).

Associated treatments (Box 86.3)

Speech therapy

Speech therapy may provide substantial help in rehabilitation of this communication handicap. Patients can be taught speech reading as lip movements and facial expressions provide assistance in semantic analysis of a sentence where unheard words are missing. Patients with severe hearing losses also perceive benefit from auditory training, which improves their recognition of key words and environmental noises.[49]

Correction of visual defects

Visual rehabilitation is an important part of global care of the elderly. Visuoauditive interactions play a prominent role in rehabilitation of severely hearing impaired subjects, which manifest particularly in lip-reading activity. A study by Rouger *et al*. showed that cochlear implanted subjects maintained their lip-reading abilities even 5 years after the cochlear implantation and that multisensorial integration facilitated their speech comprehension with speech recognition scores reaching 100% in audiovisual condition.[50]

Conclusion and the future

Hearing impairment is a common and potentially severe handicap among the elderly population. Although its adverse effects on quality of life and general medical condition are now well documented, age-related hearing loss remains underdiagnosed and insufficiently rehabilitated. Simple screening methods, such as the HHIE-S questionnaire, are available and effective and should be used in everyday geriatric exercise. In cases of mild to moderate hearing loss, various types of hearing aids may be proposed and are reasonably expected to improve quality of life. A cost reduction would probably encourage more people to search for audiology services expertise. If hearing loss is more severe, speech therapy may represent an additional help and cochlear implants have been shown to be safe and efficient in elderly people. Future directions for research include the evaluation of local interventions into the inner ear, such as cell- or gene-based therapies or drug delivery such as steroids or antioxidants. Atoh1-expressing viruses have been shown to produce some structural and functional recovery in the cochlea of deafened guinea pigs[51] and transtympanic dexamethasone[52] is regularly evaluated in tinnitus or sudden hearing loss treatment. The development of new cochlear implants, allowing local drug delivery, has already begun and seems to maintain the remaining hearing function. In the same field, cochlear implants have recently been evaluated in the treatment of unilateral tinnitus associated with deafness

and would provide significant improvements in quality of life indices.[53] In the coming years, demographic shifts will make hearing loss one of the main challenges in public health. Substantial investments from governments and industry are especially needed to promote hearing research and to develop curative solutions for hearing loss.

Key points

- Age-related hearing loss is the third most prevalent chronic condition in the elderly and will affect a growing number of individuals.
- Presbycusis represents the main cause but may coexist with middle ear pathologies or central disorders.
- The main non-genetic risk factors for age-related hearing loss are arterial hypertension, noise exposure and ototoxic drugs and should be treated or prevented. Associate conditions such as cognitive impairment or depressive symptoms should also be investigated.
- The minimal assessment in case of hearing loss should include an otoscopy, a pure-tone audiometry and a speech audiometry.
- Effective rehabilitative measures and medical, surgical and instrumental treatments are available and must be applied to reduce the handicap provoked by age-related hearing loss. These treatments should be complemented by additional care, such as consideration of isolation, speech therapy and correction of visual and cognitive deficits.

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CHAPTER 87

Disorders of the vestibular system

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Introduction

Man has developed a sophisticated system for maintaining balance, which requires the integration and modulation of visual, vestibular and proprioceptive information within the central nervous system (CNS) (Figure 87.1). Pathology of any one of the three sensory inputs or of the central vestibular pathways may give rise to disequilibrium, as may many pathological processes that affect directly or indirectly the systems essential for perfect balance (Table 87.1). Dizziness is a frequent complaint in elderly people and the prevalence of balance problems at age 70 years has been reported in 36% of women and 29% of men, increasing with advanced age to 45–51% at ages 88–90 years.[1] Dizziness and vestibular abnormalities are reported to be a major risk factor predisposing to falls among the elderly[2] and the significance of this lies in the high morbidity and mortality associated with falls in this age group. In addition, fear of falling may constitute an independent risk factor for disability, leading older people to restrict their daily living activity unnecessarily.[3] However, with the correct diagnosis, many vestibular disorders are treatable, leading to improved quality of life. Therefore, for the geriatrician, an understanding of the pathophysiology of the vestibular system and its central connections is particularly important if the common complaint of disequilibrium is to be managed successfully.

Vestibular anatomy

The inner ear is a minute, complex, fluid-filled structure surrounded by a bony labyrinth located deep in the temporal bone. The cochlea corresponds to the acoustic end-organ, whereas the vestibular end-organs consist of the three semicircular canals, the saccule and the utricle. The semicircular canals are called the *horizontal* (or *lateral*), the *posterior* and the *superior canal*. The two ends of all semicircular canals open into the vestibule, near the utricle. One end of each semicircular canal has a dilated portion, called the ampulla, containing the sensory epithelium, that is, the hair cells. The *utricle* and the *saccule* correspond to the otolith organs and both contain a small area of sensory epithelium, called maculae. All vestibular sensory epithelium is covered with a gelatinous mass, which, in the saccule and the utricle, contains calcium carbonate-rich crystals termed *otoconia*. A force parallel to the surface of the sensory epithelium provides the maximum stimulus. The semicircular canals with their ampullary tissue sense angular acceleration, whereas the saccule and the utricle sense linear acceleration. The planes of the two otolith organs lie approximately at right-angles to each other. The utricular macula is oriented roughly horizontally and the saccular macula is roughly vertical. Accordingly, the saccule is well equipped to sense vertical head acceleration and the constant pull of gravity, whereas the utricle senses linear head motion in the horizontal plane. The utricle also plays an important role in signalling the spatial upright when the head is tilted with regard to gravity. The ampullae in the semicircular canals are insensitive to the static gravitational vector or position of the head in space. However, when an appropriate angular force is introduced, the fluid in the semicircular canal is displaced along the lumen of the canal leading to changed activity in the sensory epithelium of the ampullae.

Physiology and ageing of the vestibular apparatus

In a normal subject holding the head in the anatomical position, the sensory epithelium in each ear generates resting neural activity, which passes via the VIIIth cranial nerve and the vestibular nuclei within the brainstem to the cortex.

Head movements result in linear and/or angular accelerations, which stimulate the vestibular sensory epithelium and modulate the neural activity in an equal but opposite manner in each ear. Hence an asymmetry of information is generated, which passes into the CNS. This asymmetric vestibular input allows cortical awareness of head position in space and provides the stimulus for compensatory eye and body movement.[4]

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

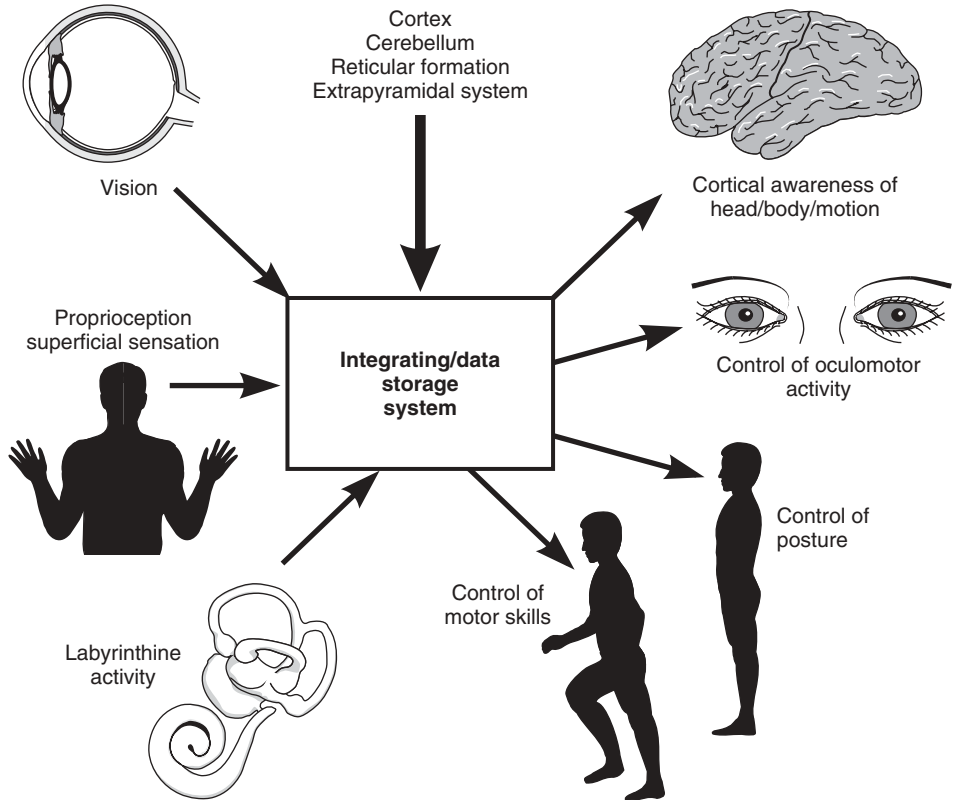

Figure 87.1 Mechanisms subserving balance in man. Reproduced from Savundra and Luxon,[4] Copyright 1997, with permission from Elsevier.

Pathology involving the peripheral labyrinth, VIIIth cranial nerve or central vestibular connections may result in an asymmetry of vestibular information, which is 'misinterpreted' by the brain and perceived as vertigo and instability. The incidence of vertigo has been reported to rise with advancing age, in parallel with the incidence of hearing loss.[5] Histopathological age-related changes reported in the human vestibular sensory organs include progressive hair-cell degeneration, otoconial degeneration in the otolith organs and decreasing number of vestibular nerve fibres.[6] In addition, age-dependent changes in both caloric and rotation test responses have been demonstrated.[5,7] However, vestibular symptoms result from an asymmetry of afferent information arising within the vestibular apparatus and degenerative changes tend to occur symmetrically. It is therefore unlikely that disequilibrium in the elderly is solely consequent upon vestibular degenerative changes and is more probably multifactorial in origin.[8] Accordingly, dizziness in the elderly is often the result of central pathology and/or sensory deficits: visual impairment (not correctable); neuropathy; vestibular deficits; cervical spondylosis; and orthopaedic disorders, interfering with joint mechanoreceptors.

Following an acute unilateral vestibular upset, the patient experiences vertigo, but usually the symptoms are relatively short lived and resolve in 6–12 weeks, as a result of processes collectively known as *cerebral compensation*. Functional recovery depends on the degree of vestibular loss and cerebral compensation. The restoration of perfect balance involves reduction or abolition of the asymmetry in postural and ocular motor tone and recalibration of the gain of dynamic vestibular reflexes, in order to ensure symmetrical compensatory vestibulospinal and vestibulo-ocular reflex action during movement of the head and body. However, in some patients recovery does not occur. The persisting symptoms are usually less dramatic and the vertigo may not be rotational, but may consist of more vague symptoms of floating, rocking or a sense of depersonalization. Such symptoms may be continuous, but may also present as episodic attacks of disequilibrium frequently triggered by an intercurrent illness or a psychological upset such as bereavement (Figure 87.2). It is well established that vestibular compensation is dependent on a variety of brainstem, cerebellar and cortical structures, together with sensory inputs including vision, somatosensory afferents and remaining labyrinthine input, which are

Table 87.1 Causes of dizziness in the elderly.

General medical	
Haematological	Anaemia
	Polycythaemia
	Hyperviscosity syndromes
Cardiovascular	Postural hypotension
	Carotid sinus syndrome
	Dysrhythmias
	Mechanical dysfunction
	Shock
Metabolic/endocrine	Hypo- and hyperglycaemia
	Thyroid disease
	Chronic renal failure
	Alcohol
Neurological	
Supratentorial	Trauma
	Neoplasia
	Epilepsy
	Cerebrovascular disease
	Syncope
	Psychogenic
Infratentorial	Vertebrobasilar insufficiency
	Subclavian steal syndrome
	Wallenberg's syndrome
	Anterior inferior cerebellar artery syndrome
	Degenerative disorders including neuropathy
	Tumour, including those of the vestibulocochlear nerves
Infective disorders	Ramsay–Hunt
	Neurosyphilis
	Tuberculosis
Foramen magnum abnormalities	
Cerebellar degeneration	
Basal ganglion disease	
Multiple sclerosis	
Otological	
Drug-induced/ototoxic	
Degenerative (e.g. positional vertigo)	
Posttraumatic syndrome	
Infection	
Vascular	
Tumours	
Menière's syndrome	
Otosclerosis and Paget's disease	
Autoimmune disorders	
Others	
Migraine	
Multisensory dizziness syndrome	

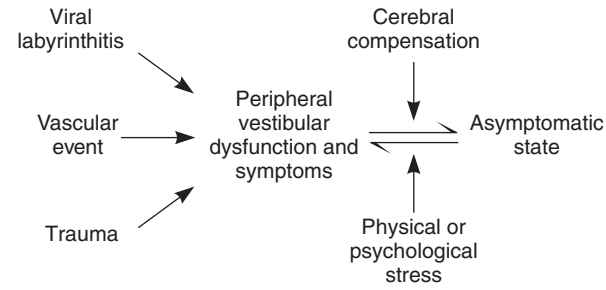

Figure 87.2 Diagram to illustrate normal sequence of events leading to recovery from a peripheral vestibular abnormality and factors relevant in decompensation.

involved in the normal perception of space, body posture and locomotion. The causes of failure of compensation or intermittent decompensation are not clear, but cerebellar damage, impairment of proprioception, visual impairment, mild cerebral dysfunction and psychological disorders have all been cited as possible contributing factors. Thus, the age-dependent changes in sensory inputs and CNS function noted above would suggest that central compensation for vestibular deficits in the elderly is likely to be less efficient.

Clinical aspects and diagnostic strategy

Vertigo, defined as 'an hallucination of movement', is a cardinal manifestation of a disordered vestibular system, whereas dizziness is a lay term, defined in the *Concise Oxford Dictionary* as 'a feeling of being in a whirl or in a daze or as if about to fall', associated commonly with a multiplicity of general medical disorders. This semantic distinction is rarely volunteered by the elderly patient, who more frequently complains of feeling faint, swimmy or lightheaded. Hence, for practical purposes, all complaints of disorientation are considered most easily within a single diagnostic approach.

History

In the history, the character, time course and associated symptoms of the dizziness/vertigo are valuable pointers in elucidating the underlying diagnosis.

Character of dizziness

Classically, the vertigo/dizziness of peripheral labyrinthine origin is manifested as acute, unprecipitated, short-lived attacks of rotational disequilibrium, associated with nausea and vomiting and more rarely diarrhoea, while the vertigo/dizziness of central vestibular origin is described as a more insidious, protracted sense of instability. Exceptions to the former include epilepsy and vertebrobasilar

artery ischaemia, and exceptions to the latter include uncompensated peripheral vestibular disorders, bilateral vestibular failure and psychogenic disequilibrium. Additional common symptoms with peripheral vestibular dysfunction are a sensation of being pulled downward or sideways or of the room tilting and a sensation of swimming, floating and lightheadedness. However, if a clear description of subjective or objective motion is given, the suspicion of vestibular pathology is raised, whereas symptoms of lightheadedness, swimminess or faintness are more likely to be attributable to a general medical/neurological disorder.

Time course

Acute rotational vertigo of less than 1 min duration is most commonly associated with the diagnosis of benign positional vertigo of paroxysmal type (see the following text), whereas acute rotational vertigo of less than 1 h duration may suggest the diagnosis of vertebrobasilar insufficiency. Vertigo of several hours' duration (less than 24 h) is most commonly associated with migraine and Menière's disease (see the following text). Acute rotational vertigo of several days' duration, with gradual resolution of symptoms, points to a viral or vascular vestibular neuritis, although persistence of such symptoms in the elderly patient may indicate poor compensation from a peripheral vestibular insult or a fixed neurological deficit as a result of a vascular event within the brainstem. Apart from the duration of the vertigo, the time course of the episodes is also of diagnostic value. A single acute episode with gradual resolution over days or weeks would point to a peripheral vestibular pathology, such as a viral neuritis or an ischaemic event. In the elderly patient, cerebral plasticity is reduced, as noted previously, hence compensation from such a single insult may be protracted and intercurrent illness may result in an exacerbation of symptoms (decompensation). Repeated short episodes with complete and rapid recovery in between would suggest migraine, Menière's disease or, most commonly, benign positional vertigo. It should be emphasized that in these conditions, the episodes also tend to occur in clusters, with intervals of months or even years of freedom.

Associated symptoms

Within the labyrinth and VIIIth cranial nerve, the vestibular and cochlear elements are in close anatomical proximity. Hence pathology in these sites gives rise commonly to both cochlear and vestibular symptoms. Frequently, the elderly patient will not volunteer a complaint of tinnitus or hearing loss, as they attribute the symptoms to their age, and it is therefore important to enquire specifically. Within the CNS, the vestibular and auditory pathways diverge and vestibular symptoms of brainstem or cerebellar origin are rarely associated with cochlear symptoms, but commonly associated with neurological symptoms and signs. Loss of vestibular function leads to impaired gaze stabilization during fast head movements, that is, *oscillopsia*.[9] Typically, the patients complain of blurred vision or bouncing images while walking or riding in a car. The vestibular system is sensitive to fast, high-frequency head movements (1–10 Hz) and cortical–optokinetic reflexes are too slow to compensate for this functional loss above 2–3 Hz. Many patients with vestibular dysfunction report a worsening or triggering of dizziness with certain visual stimuli, such as rapidly changing images, fast-moving traffic, crowds and striped material. This symptom is called *visual vertigo*.[9] In addition, anxiety disorders, depression and panic attacks have been described in association with peripheral vestibular disease, and it is likely that in some patients vestibular dysfunction may play an important role in the aetiology of these disorders.[3]

Examination

A detailed medical examination is essential with special reference to the fundi, visual fields and acuity, a general neurological examination and examination of the cardiovascular and peripheral vascular systems. On the basis of a comprehensive history and a thorough examination, the diagnosis of many neurological and general medical disorders will be excluded. The diagnosis of vestibular disorders giving rise to vertigo/dizziness is based on a neuro-otological examination, which may be divided into the following:

- an examination of the external ear and otoscopy (to exclude infection, mass or perforated ear drum) together with clinical tests of auditory acuity/whispered voice tests and tuning-fork tests
- an assessment of vestibulo-ocular function
- an assessment of vestibulospinal function, as part of the overall balance.

Otological examination

In all patients with vertigo, particularly in ethnic minorities, immigrants and immunosuppressed patients, it is essential to exclude active, chronic middle-ear disease with labyrinthine erosion. A labyrinthine fistula should be suspected in all patients with vertigo and previous surgery for middle ear disease. Clinical tests of auditory function, including tuning-fork tests (Rinne and Weber test), are important when attempting to localize pathology, since the presence of an auditory deficit may suggest an underlying labyrinthine or VIIIth nerve pathology.

Vestibulo-ocular examination

A detailed account of vestibular physiology and pathophysiology is beyond the scope of this chapter, but a clear understanding of these subjects is essential if an informed

assessment of vestibular function and vestibular investigations are to be made.[10] As has been outlined earlier, an asymmetry of vestibular activity may result from unilateral peripheral vestibular, VIIIth nerve or brainstem pathology. This asymmetry is 'monitored' by the brain and, via the pathways subserving the vestibulo-ocular reflex, results in a slow vestibular-induced drift of the eyes in the same direction as the peripheral labyrinthine lesion. For reasons that are not fully understood, this slow drift is interrupted by rapid saccadic eye movements, which are generated within the brainstem in the opposite direction. This combination of slow and fast eye movements is known as *spontaneous vestibular nystagmus* and is characteristic of acute peripheral vestibular lesions. Initially, the nystagmus present with fixation but is more prominent without fixation. As a general rule, nystagmus with fixation (nystagmus seen on routine neurological examination) disappears within 1–2 weeks after the acute lesion. By contrast, spontaneous nystagmus can be observed without optic fixation, using Frenzel's glasses, for as long as 5–10 years after the acute episode. Spontaneous vestibular nystagmus will usually beat away from the affected side, unless the lesion is irritative (infection or tumour). By definition, for clinical purposes, the direction of the nystagmus is defined by the fast phase. Thus, a right peripheral vestibular lesion gives rise to horizontal left beating nystagmus, which obeys Alexander's law. This states that the nystagmus is always in one direction irrespective of direction of gaze and that the intensity of the nystagmus is greatest when the eyes are deviated in the direction of the fast phase. For purposes of accurate review, nystagmus should be described in the following terms: primary nystagmus describes nystagmus which is beating in the same direction as gaze deviation; secondary nystagmus describes nystagmus in the midposition of gaze; and tertiary nystagmus describes nystagmus which is beating in the opposite direction to the direction of gaze (e.g. to the right, when the eyes are deviated to the left). Bidirectional nystagmus (e.g. first-degree nystagmus to the right on looking to the right and first-degree nystagmus to the left on looking to the left), vertical nystagmus (i.e. upbeat nystagmus and/or downbeat nystagmus) and dysconjugate nystagmus (a differing nystagmic response in each eye) indicate CNS disease, requiring further investigation. Clinically, *spontaneous nystagmus* should be sought in every patient complaining of dizziness/vertigo. The eyes should be examined in the midposition of gaze, with eyes 30° to the right and 30° to the left. Care must be taken that this angle is not exceeded, otherwise physiological end-point nystagmus may be observed and this may be confused with pathological nystagmus. In addition, vertical nystagmus with the eyes 30° upwards and 30° downwards should be sought.

The *head thrust test* is a quick and simple clinical test used to assess failure of the vestibulo-ocular reflex (Figure 87.3).[11] The head thrust test is positive for the side that causes the corrective saccades, indicating a vestibular hypofunction on the same side.

The presence of *positional nystagmus* is a most valuable and most frequently overlooked sign and should be sought by a briskly performed *Hallpike manoeuvre* (Figure 87.4). The patient is made to sit close to the top end of a flat examination couch. The head is held firmly between the examiner's hands and turned 30–45° to the right or left. The patient is then carried rapidly backwards with the head over the edge of the couch and the eyes are carefully observed. If nystagmus develops, it is observed until it disappears or for 2–3 min, until it is clear that the nystagmus is persistent. The patient is then returned to the upright position

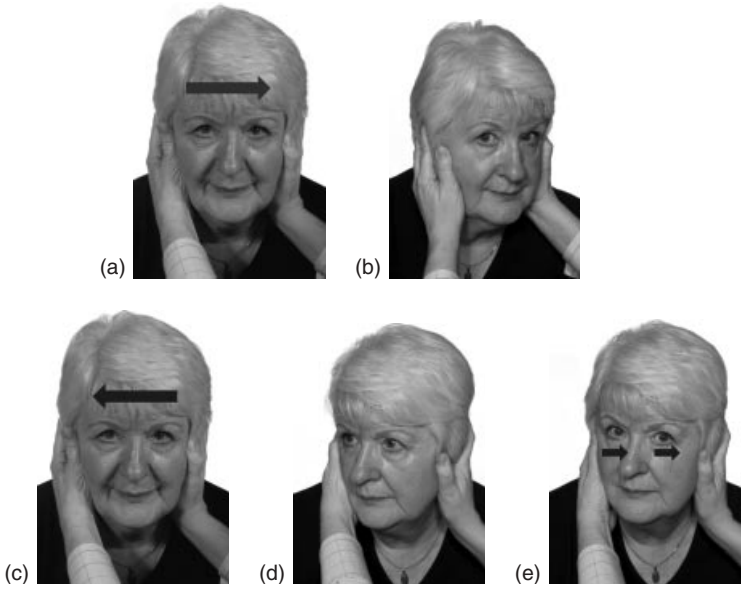

Figure 87.3 Head thrust test: normal to the left (a) and (b), abnormal to the right (c)–(e). (a), (c) Starting position with subject's head in mild cervical flexion and eye's focused on target; for example the examiner's nose. (b) On thrust of the head to the left; subject's eyes remain on target. (d) On thrust of the head to the right; the eyes move with the head and lose the target. (e) Saccadic corrections of the eyes required to bring visual focus back to target. Large arrows: direction of thrust of the head. Small arrows: direction of corrective eye saccades.

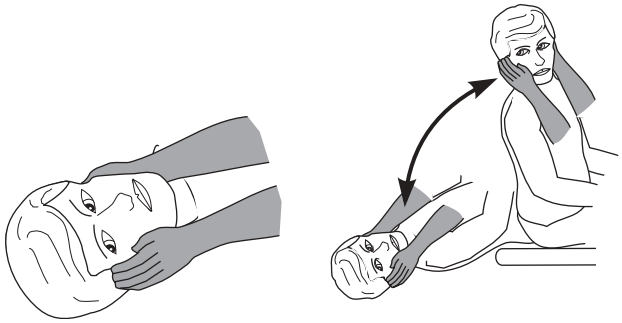

Figure 87.4 The Hallpike manoeuvre for inducing positional nystagmus.

Table 87.2 Characteristics of positional nystagmus.

	Benign paroxysmal type	Central type
Latent period	2–20 s	None
Adaptation	Disappears in 50 s	Persists
Fatigue ability	Disappears on repetition	Persists
Vertigo	Always present	Typically absent
Direction of nystagmus	To undermost ear	Variable
Incidence	Relatively common	Relatively uncommon

and the procedure repeated in the opposite direction. In broad clinical terms, the positional nystagmus which may develop can be divided into two main types, as identified in Table 87.2, although there are cases which do not clearly fit into either category and those should be investigated, as should the 'central' category, for neurological disease. If the positional nystagmus is of peripheral labyrinthine origin, after a latent period of a few seconds in the head-back position, severe vertigo develops which lasts for less than 1 min, but during which the patient may feel extremely distressed and nauseated. The nystagmus is rotatory in nature and directed towards the undermost ear. Symptoms and signs adapt and fatigue on repeated testing. Therefore, care must be taken that the procedure is carried out correctly at the first attempt. Moreover, it is important to establish this condition, as it is a troublesome cause of vertigo for which highly effective treatment is available (see the following text).

The vestibular system, via the vestibulo-ocular reflex (VOR), provides one system for the control of eye movements and gaze stability. Visual stimuli provide another mechanism for stabilizing gaze, that is, smooth pursuit and optokinetic reflexes and in general all three systems interact to produce precise and accurate eye movements. Under certain circumstances the visual and vestibular inputs to eye movement control may conflict. For example, watching a tennis tournament, as the head turns to the right to follow a ball flying through the air, the vestibulo-ocular reflex would tend to result in a compensatory eye movement to the left, whereas the subject wishes to keep the eyes fixed on the ball moving to the right. In this situation, the visual stimulus overrides the vestibular stimulus by modulation of neural activity at the level of the vestibular nuclei. This is known as *visual suppression of the vestibular responses* and clinical examination of this function allows assessment of central vestibular integrating ability. The simplest clinical means of assessing vestibulo-ocular reflex suppression is by observing the effect of optic fixation upon rotationally induced vestibular nystagmus. This may be simply accomplished in the clinic by observing the patient's eyes, while the patient is oscillated on an office chair while fixating his/her own thumbs.[9] If the eyes remain fixated on the target, VOR suppression is intact. In contrast, if clear nystagmus is elicited by the rotation, VOR suppression is abnormal, indicating CNS pathology.

Vestibulospinal assessment

Vestibulospinal function cannot be assessed in isolation and tests are non-specific and insensitive, compared with tests of vestibulo-ocular function, but tests of stance and gait may provide an indication of the extent of the patient's disability and interaction of vestibulospinal activities with other systems. The *Romberg test* is performed by asking the patient to stand in the upright position with feet together, arms by the side and eyes closed. A tendency to sway to one side usually suggests peripheral vestibular pathology, whereas an inability to stand with the feet together is more characteristic of cerebellar ataxia. Baloh *et al*.[12] demonstrated that there is a marked increase in postural sway in elderly patients with unilateral vestibular hypofunction, in comparison with younger patients with the same disorder. Anxious elderly patients frequently tend to fall backwards like a wooden soldier and this is indicative of a non-organic component to their symptoms, but it must be emphasized that this is almost always observed in the presence of an underlying abnormality, which will be elucidated on full examination. *Gait testing* is assessed by asking the patient to walk towards a fixed point in a normal manner, but with eyes closed. Again, a tendency to veer in one direction is most commonly the result of an ipsilateral peripheral vestibular disturbance, but may on occasions be observed with cerebellar disease. This latter diagnosis is most commonly associated with a broad-based, ataxic gait. Having briefly reviewed vestibular physiology and pathophysiology and outlined the aspects in the history and examination, which may enable the clinician to identify a vestibular abnormality, the remainder of this chapter will be devoted to a review of the more common causes of vestibular pathology in the elderly and the therapeutic options available.

Peripheral vestibular disorders

Viral vestibular neuritis

Single episodes of acute rotational vertigo associated with nausea and vomiting, with or without cochlear symptoms, occur in all age-groups. The attacks are usually unprecipitated, but may be preceded by an upper respiratory- tract infection, and are therefore presumed to be of viral origin, although there is little definitive evidence for this.[13] Additional possible causes of vestibular neuritis include other infectious agents and vascular or immune-mediated disorders. The vertigo may last for a few hours or several days and the patient may then be extremely unsteady for a period of weeks, during which time cerebral compensation produces a degree of symptomatic recovery. However, in the elderly patient, the plasticity of the CNS is compromised and recovery is often slower and is rarely complete.

Ramsay–Hunt syndrome (see Chapter 117, Infections of the central nervous system)

The Ramsay–Hunt syndrome or herpes zoster oticus is an example of a mononeuritis of the VIIth cranial nerve. The patient experiences a deep, burning pain in the ear, which is followed within a few days by a vesicular eruption in the external auditory canal and on the concha. The patient often develops facial paralysis. In addition, some patients present with hearing loss, tinnitus, vomiting, vertigo and nystagmus indicating VIIIth nerve involvement.

Bacterial infection

Chronic middle-ear disease is a prevalent condition in the elderly and it cannot be overemphasized that in any patient with vestibular symptoms in whom there is the slightest suspicion of middle-ear disease or history of previous middle-ear surgery, the presumptive diagnosis must be of labyrinthine erosion. *Perilymph fistulae* may result from bony erosion by cholesteatoma with the lateral semicircular canal being the most commonly affected site.[14] Rarely, perilymph fistulae may be caused by barotraumas, syphilitic osteitis, tuberculous otitis media, chronic perilabyrinthine osteomyelitis or glomus jugulare tumour. *Otitis externa* is a common benign disorder, but in debilitated elderly patients, particularly those with diabetes and other immunosuppressive conditions, it may present in a more malignant form. The causative organism is mainly *Pseudomonas aeruginosa*. The disease spreads rapidly, invading surrounding soft tissues, cartilage and bone structures, with occasional involvement of adjacent cranial nerves, causing hearing loss and vertigo. Prolonged treatment with effective antibiotics, carbenicillin or gentamicin, has improved the previously poor prognosis.

Neoplasia

Vestibular disorders as a direct result of neoplasia are uncommon, even in the elderly. The non-metastatic complications of carcinomatous encephalomyelitis may involve the vestibular nerve, while cochlear and vestibular symptoms have been reported in patients with carcinomatous meningitis.[15] Secondary tumour involvement of the inner ear by blood-borne metastases from hypernephroma and lung, prostate, breast and uterine carcinoma have been reported and direct extension of nasopharyngeal carcinoma may occur. Aural tumours are rare, with the exception of cholesteatoma, as outlined previously. Cochlear symptoms (tinnitus and hearing loss) are the most common presenting symptoms of *acoustic neurinoma* (vestibular Schwannoma), but 10% of patients complain of vertigo, dizziness and/or unsteadiness. A unilateral asymmetric hearing loss must be investigated and brainstem auditory-evoked responses provide the best screening technique. If these are abnormal, a computed tomography (CT) scan or, preferably, a magnetic resonance imaging (MRI) scan, should be obtained. The diagnosis and management of this condition in the elderly do not differ from those of any other patient and early diagnosis is essential, as excellent surgical results are achieved with small tumours (<20 mm in size). However, it has been shown that small tumours do not invariably enlarge with time and the high sensitivity of MRI may mean that clinically insignificant tumours may be detected. In the elderly patient, it is appropriate to monitor the growth of small acoustic neuromas (vestibular Schwannoma), but this must be balanced against the significantly decreased mortality/morbidity associated with surgery for smaller tumours.

Vascular disorders

Both the peripheral and central vestibular apparatus are supplied by the vertebrobasilar circulation and, as cerebrovascular disease is common in developed countries (the risk factors being diabetes mellitus, hypertension and a raised haematocrit), disequilibrium in the elderly is commonly ascribed to vascular pathology. Ischaemia of the internal auditory artery may give rise to three differing clinical syndromes: vestibular disorders alone, cochlear disorders alone or combined vestibulocochlear symptomatology. An isolated acute episode of rotational vertigo, as outlined in the description of viral vestibular neuritis, may be of vascular origin, but recurrent isolated vertigo is rarely of vascular origin. The diagnosis is usually presumptive and is based on evidence of vestibular dysfunction in a patient with other manifestations of vascular disease. Risk factors (diabetes mellitus, hyperlipidaemia, hypertension, myxoedema) should be sought and treated appropriately.

Trauma

The elderly are particularly prone to falls and vestibular abnormalities as a result of even trivial head injury are now well recognized.[16] Damage to the vestibular system may be the result of direct injury, for example, labyrinthine concussion and/or temporal bone fracture, or of secondary shearing forces in the brainstem and cerebellum. Falls may cause cervical trauma in the elderly, which may also give rise to vestibular disturbances.[16]

Two post-traumatic vestibular syndromes may be identified, as follows.

Unilateral auditory and vestibular failure

This is associated with transverse fractures of the temporal bone, in which severe vertigo and hearing loss are accompanied by bleeding from the ear, nausea and vomiting. The patient prefers to lie completely still with the affected ear uppermost. Over a period of 6–12 weeks there is marked improvement in the disequilibrium related to cerebral compensation, although in the elderly patient, as noted earlier, this may be slower and less complete than in a younger person. There is no recovery of the auditory deficit.

Benign positional vertigo of paroxysmal type

This is the most common clinical syndrome after head injury, but may also be seen in the elderly as an idiopathic disorder or secondary to vestibular neuritis. Recent work has led to the theory of canalithiasis (Figure 87.5), which explains the majority of the characteristic features of benign positional nystagmus.[17, 18] This theory proposes that debris from the otolith organ lies in the most dependent portion of the posterior canal and, upon assuming the critical head position, the clot moves in an ampullofugal direction and, thus, has a 'plunger' effect within the narrow posterior semicircular canal. This causes movement of the cupula in an ampullofugal direction, with a brief paroxysm of vertigo and nystagmus as a result.

The clinical course of post-traumatic benign positional vertigo is that some days or weeks after even a trivial head injury, momentary, short-lived episodes of vertigo occur on assuming specific head positions, particularly associated with neck extension and typically appearing when lying down on one ear, bending forwards or looking up. Frequently, the only abnormal clinical sign is benign positional nystagmus of paroxysmal type on performing the Hallpike manoeuvre (see above). The vertigo associated with this condition is particularly severe and the elderly patient is frequently extremely afraid, as the attacks are very sudden and may cause a drop to the ground and vomiting. This leads to anxiety, partly from fear of embarrassment if this should happen in a public place, and partly from fear of being incapacitated at home, unable to reach help. Not infrequently, this diagnosis is overlooked and the clinician merely observes an extremely anxious elderly patient, who finds difficulty explaining such brief yet severe symptoms. It is therefore extremely important that the Hallpike manoeuvre is performed and a clear explanation of the benign nature of the condition given. In 1980, Brandt and Daroff[19] reported complete relief of symptoms in 66 of 67 patients with benign positional vertigo as a result of precipitating head positions 'on a repeated and serial basis'. They suggested that the mechanism of improvement using this therapy lay in rapid and aggressive vertigo-provocative movements, which loosened and dispersed otholitic debris from the cupula of the posterior semicircular canal (cupulolithiasis) (Figure 87.5). However, on the basis of our current knowledge, it seems more likely that these manoeuvres cleared debris from the most dependent part of the posterior semicircular canal into the utricle, where they no longer interfered with semicircular canal dynamics. More recently, single positional manoeuvres[20] have been described in which specific movements of the head allow the offending debris in the posterior canal to be moved by gravitation into the utricle: the *Epley manoeuvre* (Figure 87.6). The patient is instructed to sit upright for 48 h after this procedure, which has been reported to be effective in 80–85% of patients in the first attempt at treatment and in a further 10% upon a second attempt. Relapses may occur, but the manoeuvre should then be repeated. Pretreatment sedation is not required except for the most anxious of patients and the manoeuvre is as effective in older people as in younger people. In a small percentage of patients, it would appear that the particle repositioning procedures are not effective and, in intractable cases, plugging of the posterior semicircular canal or section of the posterior and ampullary nerve should be considered.[21]

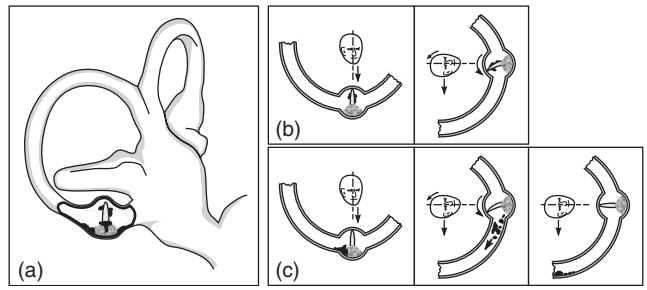

Figure 87.5 Diagram to illustrate the pathophysiological mechanisms of cupulolithiasis and canalithiasis. (a) Illustration of cupula in ampulla of posterior semicircular canal, with debris attached to and surrounding the cupula. (b) Illustration of the effect of gravity on the cupula and debris as proposed by the theory of cupulolithiasis. (c) Illustration of the effect of gravity on the cupula and debris as proposed by the theory of canalithiasis. Reproduced from *Vestibular Research*, vol. 3, Brandt T and Steddin S, pp. 373–82, Copyright 1993, with permission from IOS Press.

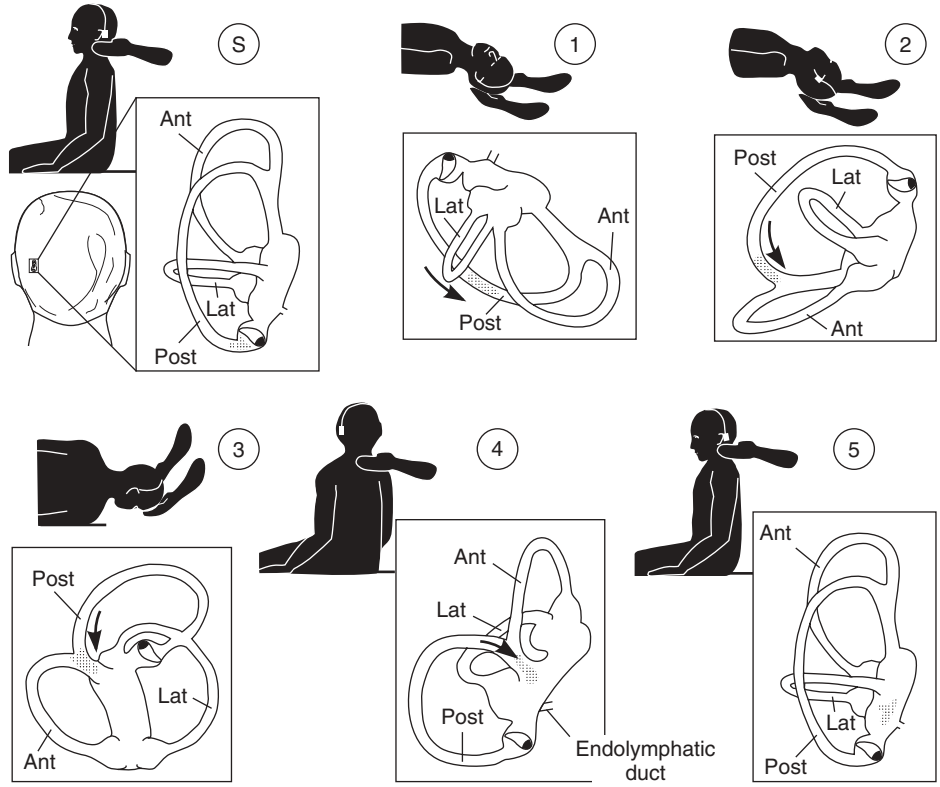

Figure 87.6 Diagram to illustrate particle repositioning procedure for canalithiasis of left posterior semicircular canal, as described by Epley.[20] S, sitting; 1 – 5, Stages of manoeuvre. Semicircular canals: Ant, anterior; Post, posterior; Lat, lateral. Reproduced from Epley,[20] Copyright 1992, with permission from Elsevier.

Menière's disease

Menière's disease was first described in 1861 by Prosper Menière and is characterized by episodic vertigo, low-frequency hearing loss with tinnitus and aural fullness. Menière's disease does occur in the elderly[22] and the pathological underlying process is thought to be due to an increase in endolymph volume, that is, endolymphatic hydrops. Treatment remains empirical but routinely consists of a salt-free diet and diuretics, which is effective in most patients. In intractable cases with incapacitating vertigo, intratympanic gentamicin injection or surgical intervention (e.g. vestibular neurectomy and labyrinthectomy) may be considered.

Iatrogenic vestibular dysfunction

Iatrogenic dizziness may be surgical or medical in origin and it is well established that otological surgery carries a risk of inducing dizziness/vertigo postoperatively. Moreover, vestibular disturbances after non-otological surgery have been documented. Drug-induced dizziness is a very significant problem in the elderly and many, if not all, drugs may produce dizziness, although it is often impossible to identify the underlying mechanism causing disequilibrium. Anaemia secondary to gastrointestinal bleeding, hypoglycaemia, cardiovascular effects including reduction in cardiac output, dysrhythmias and postural hypotension and ototoxicity should all be considered. The most common drugs giving rise to dizziness in the elderly are shown in Table 87.3.

Ototoxic damage is of particular importance, as it is irreversible. The vestibulotoxic effect of the aminoglycoside antibiotics is common knowledge and in the elderly they should be used only as a lifesaving measure. It is well established that age is an important factor in the susceptibility to aminoglycoside ototoxicity and for this reason blood levels of these drugs should be measured meticulously in the elderly, especially in the presence of concurrent diuretic therapy and/or any change in the overall medical state. However, the correlation between blood levels of the ototoxic drug and ototoxic effect can be poor, due to interindividual differences and a possible accumulation of the drug in the inner ear fluids. Although standard vestibular tests are not feasible in a severely ill patient, recent methods of assessing vestibular function at the bedside have been developed and are of particular value in potential ototoxicity.[9, 11, 23]

Table 87.3 Drugs causing dizziness/vertigo[a].

Psychotropic drugs	
Antidepressants	Tricyclics, MAOIs, SSRIs
Tranquilizers	Benzodiazepines, phenothiazines
Anticonvulsants	Phenytoin, carbamazepine, gabapentine, lamotrigine
Analgesics	Paracetamol, acetylsalicylate, NSAIDs, opioids
Cardiovascular drugs	
Antihypertensives	Diuretics (thiazides and loop), β-blockers, calcium-channel blockers, ACE inhibitors, methyldopa, hydralazine
Anti-arrhythmic	β-Blockers, verapamil, mexiletine, flecainide, amiodarone, disopyramide
Anti-angina	Nitrates, calcium-channel blockers, β-blockers, potassium-channel activators
Antimicrobials	Aminoglycosides, tetracyclines, macrolides, chloroquine, isoniazid
Anti-allergic drugs	Non-sedating and sedating antihistamines
Hormone replacement/ substitute	Hypoglycaemics, corticosteroids, HRT
Chemotherapeutic agents	Cisplatin, busulfan, cyclophosphamide, vinblastine, methotrexate

[a]MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin-converting enzyme inhibitors; HRT, hormone replacement therapy.

Central vestibular disorders

Cerebrovascular disease

Cerebrovascular disease is most commonly secondary to atheroma, although giant cell arteritis should be considered in the elderly. The vertebrobasilar circulation supplies the peripheral vestibular apparatus as described earlier, but also supplies the vestibular nuclei. These nuclei occupy a large area in the lateral zone of the brainstem and are particularly susceptible to a reduction in the blood flow of the main basilar artery and the cerebellum, which is extremely important in modulating information required for balance at the level of the vestibular nuclei. The vertebral and internal carotid arteries provide the brain with a rich blood supply and the terminal branches anastomose to form the circle of Willis. This forms an anatomical safeguard against ischaemia arising from narrowing of one vessel and, in addition, there are autoregulatory mechanisms within the cerebral circulation protecting it from fluctuations in the systemic blood pressure. Nonetheless, cerebrovascular disease is one of the most common causes of chronic disability and death. In addition, white-matter changes due to vascular ischaemic damage produce gait disorders and also cognitive impairment, both of which predispose to falls.

Vertebrobasilar artery ischaemia

Episodic vertigo in an elderly patient is commonly ascribed to vertebrobasilar insufficiency, in the knowledge that cerebrovascular disease is common in the elderly and also on the basis that vertigo and/or dizziness have been reported as the first and most frequent symptom of this condition.[24, 25] The classical symptoms of vertebrobasilar insufficiency include dizziness/vertigo, dysarthria, numbness of the face, hemiparesis, headache, dysphagia, sensory disturbance, cerebellar ataxia and visual disturbances. The diversity of symptoms and signs reflects the close proximity of cranial nerve nuclei and motor and sensory tracts, within the small confines of the brainstem. The duration of transient ischaemic attacks in the vertebrobasilar territory may be variable, but by definition must be without actual infarction and less than 24 h. They may recur at variable intervals and may or may not be stereotyped.

Classical attacks of vertebrobasilar artery ischaemia associated with vertigo do not present a diagnostic problem. In this context, it is important to emphasize that dizziness or vertigo, accompanied by only VIIIth nerve manifestations, is unlikely to be of vascular origin. Moreover, tinnitus and deafness are unusual manifestations of vertebrobasilar ischaemia and, if present, are almost always accompanied by other symptoms and signs of brainstem involvement. Despite the presence of vestibular and oculomotor abnormalities in vertebrobasilar ischaemia, no characteristic pattern of neuro-otological findings has emerged in this disorder. Hence isolated episodes of rotational vertigo in an elderly patient should not be ascribed to vertebrobasilar insufficiency, unless there is other neurological evidence to support this diagnosis.

Completed strokes (see Chapter 57, Acute stroke care and management of carotid artery stenosis)

Completed strokes in the vertebrobasilar territory may involve the vestibular nuclei and there are a number of well-recognized syndromes. The Wallenberg or lateral medullary syndrome may result from occlusion of the posterior inferior cerebellar artery or the vertebral artery.[24] The syndrome is characterized by acute rotational vertigo with nausea and vomiting and ipsilateral dissociated sensory loss in the distribution of the facial nerve, together with contralateral truncal loss and ipsilateral cerebellar ataxia, bulbar palsy and Horner syndrome. Specific visuo-vestibular abnormalities have been identified with Wallenberg syndrome, including spontaneous rotatory nystagmus, with the fast phase directed towards the normal side, tonic deviation of the eyes towards the side of the lesion, with loss of fixation, voluntary and

involuntary saccades of larger amplitude in the direction of the lesion and asymmetry of smooth pursuit, optokinetic and vestibular responses as a result of the interaction between spontaneous nystagmus and/or slow eye movements. Pontine/medullary and cerebellar haemorrhages may involve the vestibular apparatus. In the former, there are multiple brainstem signs and vertigo is usually a fleeting event, although a common presenting symptom, before the patient becomes unconscious. Cerebellar haemorrhage presents with acute vertigo, vomiting and an inability to stand, in the presence of cerebellar signs. The importance of rapid diagnosis lies in the ability to correct this condition surgically. Without rapid intervention, the patient dies from brainstem compression.

Cervical vertigo

Cervical vertigo is defined as vertigo induced by changes of position of the neck in relation to the body.[26] There is much controversy as to the underlying pathophysiology of cervical vertigo, but sympathetic irritation resulting in vertebrobasilar ischaemia, intermittent vertebral artery compression by osteophytes caused by cervical spondylosis and deranged sensory input from the cervical kinaesthetic receptors have been postulated. It is a widely held belief, particularly in the elderly, that vertigo and nystagmus may result from vertebrobasilar ischaemia, secondary to compression of blood vessels, as a result of arthritic changes in the neck. This seems unlikely noting the observations that unilateral, or indeed bilateral, compression of the vertebral arteries in the presence of a normal circle of Willis and internal carotid arteries produces only minimal brainstem ischaemia. It should be emphasized that radiological findings may prove misleading, as osteoarthritic changes in the cervical vertebrae are common in the elderly and not directly related to symptomatology. Neuro-otological tests in patients suspected of having cervical vertigo are frequently normal and no specific assessment objectively defines the condition. The diagnosis will be facilitated with the development of a specific test defining specific abnormalities.

Neoplasia

Dizziness and/or vertigo are early or initial symptoms in 25% of brainstem tumours. In later life, metastases are the most common neoplasms involving the brainstem and/or cerebellum, which give rise to vestibular dysfunction. Brainstem lesions typically present with progressive cranial nerve palsies together with long tract signs, whereas midline cerebellar lesions give rise to truncal ataxia and oculomotor abnormalities, including impaired smooth pursuit, saccadic dysmetria and rebound nystagmus.[4] Hemispheric cerebellar lesions cause ataxia of the ipsilateral limbs with truncal ataxia. Temporal lobe tumours give rise to 'disequilibrium' more frequently than in any other cortical site. This is not surprising as the temporal lobes exert a modifying influence upon the vestibular nuclei. Cerebellopontine angle lesions and, in particular, acoustic neurinomas (vestibular schwannomas) have been mentioned above, but are a rare cause of vestibular symptoms. Acoustic neurinomas (vestibular schwannomas) arise mainly on the vestibular division of the VIIIth cranial nerve and as they expand in the cerebellopontine angle, there is involvement of the Vth and VIIth cranial nerves, together with ipsilateral cerebellar signs and ultimately lower cranial nerve involvement. If surgical intervention is not undertaken, brainstem compression results in death.

Infection

Although tuberculosis is no longer a common disorder in developed countries, the possibility of a tuberculoma in the brainstem, cerebellopontine angle or temporal lobe should be borne in mind, especially in elderly immigrants and in elderly, debilitated or alcoholic patients. Neurosyphilis may involve the vestibular apparatus at all stages of the disease.[27] A high index of suspicion is necessary if rare cases in the elderly are not to be missed.

Neurological conditions

Many neurological disorders may affect the central vestibular connections and a discussion of each is beyond the scope of this chapter. In the elderly, of special note are Parkinson's disease, cerebellar disease and multisystem atrophies. Migraine is an important cause of various forms of episodic vertigo and may occur at any time throughout life.[28] The vertigo may last a few minutes or several hours and in 32% of patients vertigo and headache are not contemporaneous. The symptoms often resolve with effective antimigrainous treatment. The importance of the cerebellar connections on the vestibular system in terms of maintaining balance and eye position has been emphasized. Neuro-otological abnormalities in cerebellar disease are well defined.[29] Cerebellar degeneration may be seen in the elderly in association with malignancy (paraneoplastic syndrome), phenytoin intoxication, hereditary ataxias, alcoholism and myxoedema. Early diagnosis may lead to effective treatment in these groups. Of importance in the elderly, Paget's disease may give rise to basilar impression which may be accompanied by vertigo. The neurological symptoms produced by spinal cord and cerebellar compression together with obstruction of the fourth ventricle usually overshadow the vestibular disorder.

This review of vestibular disorders in the elderly has concentrated on the more common vestibular pathologies affecting this age group, but it must be emphasized that

any vestibular disorder may occur and conditions such as endolymphatic hydrops, migraine and multiple sclerosis should not be overlooked.

Management

The initial management of a patient must be directed at establishing the presence of an underlying diagnosis for which specific treatment may be instituted. A number of elderly patients will be found to have minor visual impairment, which should be corrected if possible. If there is proprioceptive impairment that is predominantly in the lower limbs, it may be helpful to provide a walking stick to obtain additional proprioceptive information through the upper limbs. In addition, assistive devices and interventions for preventing falls should be considered. The management of peripheral vestibular dysfunction consists in counselling and vestibular rehabilitation exercises.[30] Drug therapy may be of value in the management of acute vertigo, but has no place in the long-term management of chronic vestibular symptoms, as it delays compensation. Symptoms of disequilibrium are especially disturbing for the elderly, not only because they fear some sinister pathology but also because they are terrified of the consequences of repeated attacks of vertigo during which they may be unable to summon outside assistance. It is therefore extremely important to obtain a detailed history, carry out a full examination and appropriate investigations and give a simple and clear explanation of the underlying cause of symptoms of disequilibrium and the therapeutic options that are available. Chronic vestibular symptoms may be caused by central vestibular pathology or uncompensated peripheral vestibular disorders. The management of central vestibular dysfunction remains poorly understood, but a trial of cinnarizine, clonazepam, baclofen, gabapentin or carbamazepine may prove of value. The sedative side effects of these drugs should be recalled in the elderly and the dose titrated against sedation. In patients with a sense of instability and falls, which are frequently associated with basal ganglia disorders and cerebellar disease, physiotherapy to teach alternative gait strategies may prove invaluable in enabling the patient to regain a sense of confidence and improve their mobility.

Vertigo associated with peripheral vestibular disorders may either be attributable to specific conditions, for which there is a recognized treatment regime, or a specific aetiology may not be identified despite the evidence of peripheral vestibular dysfunction on standard vestibular tests. The treatment of specific otological disorders is no different in the elderly to any other age group and the reader is referred to standard otology texts. Persistent vestibular symptoms due to peripheral labyrinthine dysfunction are frequently amenable to vestibular rehabilitation and it cannot be overemphasized that destructive surgical procedures should not be considered, particularly in the elderly, until detailed neuro-otological investigations determining the site of lesion and exhaustive medical management have been tried. There is no reason to assume that a patient will compensate more efficiently from a total labyrinthine destruction than from a partial impairment of vestibular function, particularly when it is likely that the failure of compensation in the elderly may be due to mild central processing disorders or unsuspected psychological factors.

Acute vertigo associated with nausea and vomiting requires immediate treatment with an anti-emetic such as prochlorperazine, by buccal absorption, intramuscularly or by suppository, or metoclopramide intramuscularly, such that nausea and vomiting are alleviated. This allows the administration of a vestibular sedative, of which cinnarizine 15 mg every 8 h is the treatment of choice. Again, in the elderly patient, sedative side effects must be carefully monitored and the dose adjusted accordingly.

Chronic or recurrent vertigo, associated with poorly compensated peripheral pathology (Figure 87.7), is frequently accompanied by secondary symptoms of psychological distress (anxiety, depression and phobic symptoms), malaise, fatigue and cervical pain related to tension in neck muscles, as a result of conscious or subconscious limitation of neck movements, which are likely to precipitate an increase in vertiginous symptoms. The development of psychological symptoms in patients with disequilibrium is now well recognized,[3] and appropriate psychological support in the form of behavioural therapy or psychiatric care is essential for patients who manifest psychological symptoms if optimal vestibular compensation is to be achieved.

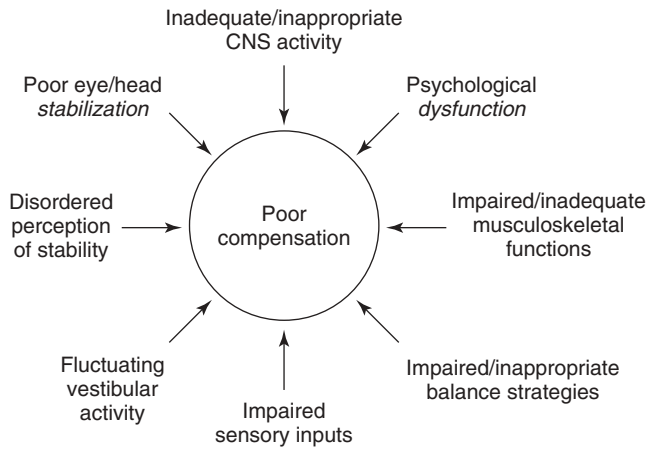

Figure 87.7 Factors predisposing to decompensation. After Shumway-Cook and Horak.[30]

This is particularly important in the elderly age group, who are more likely to be susceptible than their younger counterparts and are therefore deeply concerned by disorders that impair their physical abilities and threaten their independence.

As early as the mid-1940s, physical exercise regimes (the *Cawthorne–Cooksey exercises*) were introduced as a means of expediting recovery from peripheral vestibular disorders. These exercises are a graduated series of exercises aimed at encouraging head and eye movements, which provoke dizziness in a systematic manner and facilitate vestibular compensation. The exercises are not an endurance test and for the elderly patient it is important to modify the regime within the limits of the patient's physical abilities. The passage of time has supported the efficacy of these exercises and successful vestibular rehabilitation improves activities of daily living and reduces fall risk. Significant improvement has been shown in patients with peripheral vestibular dysfunction, but also in patients with central balance disorders. Moreover, there is no evidence that age is a negative prognostic factor. Recent work has suggested that 'customized' exercises, tailored to the individual patient, are equally effective. Specific positional manoeuvres for the management of benign positional vertigo (Epley and Semont manoeuvres) have been described earlier and form an important element of vestibular management.

A combination of canalith repositioning manoeuvre and vestibular rehabilitation has been shown to improve benign positional vertigo in the elderly. Although repositioning manoeuvre is the most effective treatment, vestibular rehabilitation can be added to improve the results in the treatment, particularly with regard to the high recurrence of positional vertigo. As noted previously, vestibular sedatives such as cinnarizine are of value in the management of acute vertigo, but have a very limited role in the management of chronic vestibular syndromes. In particular, anti-emetics such as prochlorperazine should be avoided, because of the rare but irreversible syndrome of extrapyramidal dysfunction. Moreover, psychotropic drugs should be administered only for specific psychiatric indications, as such medication may interfere with compensatory mechanisms for peripheral vestibular disorders. In the elderly, the indications for otological surgery for vestibular disorders must be carefully weighed against the general medical state of the patient and the likely extent of recovery postoperatively. Ludman's excellent review of the surgical treatment of vestibular disorders outlines the various techniques available.[21] As has already been noted, compensation may be prolonged or indeed incomplete as a result of dysfunction of the integrating ability of the CNS and/or other sensory modalities. The risk of a persisting imbalance after vestibular destruction must therefore be borne in mind.

Key points

- Do not attribute vertigo to 'age'.
- A thorough history and examination will often provide a clear direction as to diagnosis.
- Correct diagnosis allows the treatment of many of the peripheral and central vestibular disorders.
- Introduce vestibular rehabilitation/gait strategy exercises in the elderly early and aggressively.
- Destructive surgical procedures should not be considered until detailed neuro-otological investigation and medical management have been tried exhaustively.

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CHAPTER 88

Smell and taste

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Introduction

Since 1900, the percentage of Americans over the age of 65 years has more than tripled (4.1% in 1900 to over 12% in 2000) and their number has increased over eleven times (from 3.1 million to 34.9 million).[1] Given the fact that the ability to perceive odours and tastes decreases markedly with age,[2] it is not surprising that increasing numbers of elderly patients are seeking medical help for their chemosensory problem. Indeed, over half the population between the ages of 65 and 80 years, and over three-quarters beyond 80 years, have significant olfactory loss. The implications of such age-related chemosensory losses are far-reaching. Aside from being unable to appreciate fragrances, the taste of food, and the freshness of spring and the seashore, elderly persons suffering from chemosensory disorders are compromised in their ability to detect fire, leaking natural gas, toxic fumes and spoiled food. Many become depressed, and a disproportionate number die in accidental gas poisonings.[3] Others lose their lives or are severely burned in the hundreds of butane and propane gas explosions that occur each year.

It is now well documented that olfactory dysfunction is among the first, if not the first, clinical signs of Alzheimer's disease and sporadic Parkinson's disease (for review, see Hawkes and Doty[4]). Although, as described later in this chapter, smell loss has multiple determinants and is not always a harbinger for such diseases, it is incumbent upon the physician to be aware of this association. Given the dietary and safety consequences of chemosensory disturbances, it is also incumbent upon the physician to employ the most modern means available to evaluate, counsel and treat patients with chemosensory disturbances whenever possible.

This chapter provides the gerontologist with an up-to-date overview of the nature and cause of age-related chemosensory disturbances, means for evaluating such disturbances, and approaches useful for counselling patients and treating the underlying dysfunction.

Characterization of chemosensory problems

The general term for inability to smell is anosmia, and for lessened smell function hyposmia. The corresponding terms for taste are ageusia and hypogeusia. In the older medical literature, anosmia is sometimes referred to as olfactory anaesthesia or anosphrasia. In some nosological schemes, anosmia and hyposmia are classified under the general term dysosmia (distorted smell function), whereas ageusia and hypogeusia are classified under the term dysgeusia (distorted taste function). In this scheme, dysosmia includes forms of dysfunction in addition to anosmia, such as distorted smell sensations (parosmia, cacosmia) and smell hallucinations (phantosmia). Dysgeusia similarly includes both ageusia and distortions in taste function, such as strong salty or sour sensations in the absence of appropriate stimulation. Today, however, it is more common that anosmia, ageusia, dysosmia and dysgeusia are classified separately from one another, with the first two terms signifying losses, and the second two distortions, of smell and taste sensations, respectively.

Anatomy of the olfactory system

To be sensed, odorants must enter the nose and reach specialized receptors within the olfactory neuroepithelium, a patch of tissue a few square centimetres in size that lines the upper recesses of the nasal vault, including the cribriform plate and sectors of the nasal septum, middle turbinate and superior turbinate[5] (Figure 88.1). When activated, the odorant receptors open or close (e.g. via second-messenger systems) membrane channels on the cilia, resulting in a flux of ions and an alteration of the cell's resting potential that ultimate leads to an axonal action potential.[6] cAMP is the primary second messenger involved in the transduction process. cAMP amplifies the signal coming from the receptors and facilitates the release of glutamate, the main neurotransmitter of olfactory receptor cells, into the synapse.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

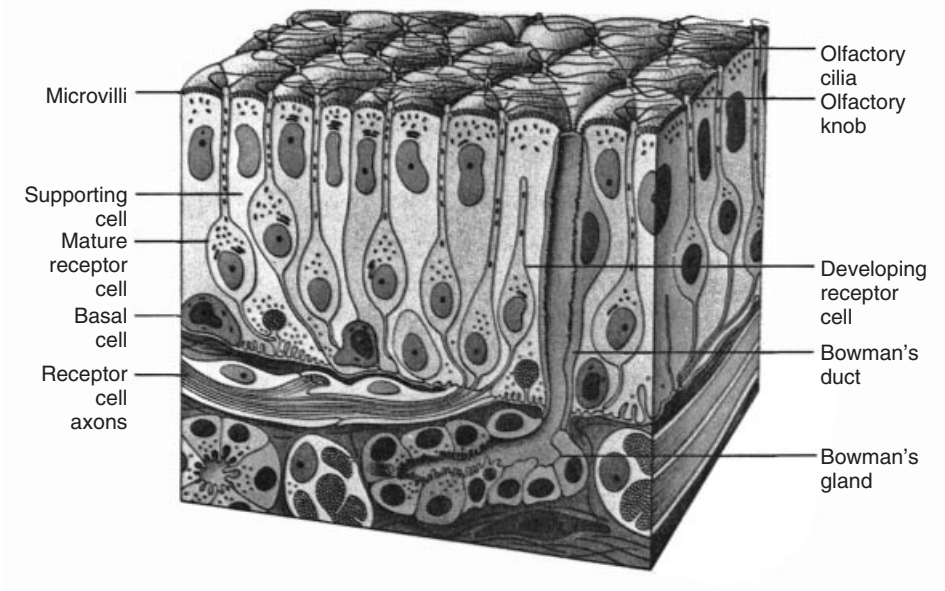

Figure 88.1 Schematic of the cellular organization of the human olfactory neuroepithelium. Not pictured are the microvillar cells, which are small goblet-shaped cells interspersed among the other cell types at the surface of the epithelium in a ratio to the mature receptor cells of 1:10. Reprinted from *Gray's Anatomy*, Warwick R and Williams PL, Copyright 1973, with permission from Elsevier.

Odorant receptor genes, whose discovery by Buck and Axel in 1991 led to the Nobel Prize for Medicine or Physiology in 2004,[7] represent the largest of all mammalian gene families, comprising nearly 3% of the more than 30 000 genes in the mouse and human genomes. Interestingly, only one type of receptor is expressed on the surface of the cilia of a given receptor cell, and odorants typically bind to more than one type of receptor. The olfactory receptor cells number 6–10 million in the adult human and are insulated from one another at the epithelial surface by sustentacular cells.[5] A blanket of mucus, which contains a number of enzymes (e.g. cytochrome P450), covers the olfactory neuroepithelium and deactivates or filters materials that absorb into the mucus, including some odorants.[8] This mucus also aids in protecting the epithelium from desiccation, heat and xenobiotic insult, and serves as a solvent and carrier for odorant binding proteins – proteins that facilitate the transport of some lipophilic molecules to the receptors through aqueous phases of the mucus.

The unmyelinated axons of the bipolar olfactory receptor cells collect into 15–20 fascicles (fila olfactoria) that collectively make up the olfactory nerve (cranial nerve (CN) I). These axons course through the cribriform plate and synapse within spherical masses of neuropile within the olfactory bulb termed glomeruli. Second order connections with the dendrites of mitral and tufted cells are made within these structures. The latter cells – the primary output cells of the olfactory bulb – project to the olfactory cortex, which includes the piriform, periamygdaloid and entorhinal cortices. These structures have extensive connections with the hippocampus, mediodorsal thalamus, hypothalamus and other brain regions, in addition to having efferent connections with cells within the olfactory bulb.[4]

Most odorants stimulate a broad range of receptor cells. Although limited sets of such cells respond to a given odorant, overlap is common and the pattern of neuronal activity across cells codes odour quality. Receptor cells that express the same receptor project to the same glomerulus, where information is further transformed. The second-order neurons – the mitral and tufted cells – send dendritic processes into the glomeruli, where they synapse with the axons of the incoming receptor cells. The axons of the mitral and tufted cell project, via the lateral olfactory tract, to the olfactory cortex, where further connections occur with structures in which perceptual elements of odours are formed; that is, perceived pleasantness and associations with environmental objects. It is noteworthy that the olfactory system differs from other sensory systems in sending projections first to the cortex rather than to the thalamus. It also is unique in the degree to which it exhibits plasticity – the olfactory receptor cells have the propensity to regenerate from stem cells within the basement membrane, and cells within the olfactory bulb, namely the periglomerular cells and the granule cells, are continuously repopulated by cells that migrate from periventricular regions along the rostral migratory stream. Because olfactory receptor cells directly project from the environment of the nasal cavity into the brain, they are a major conduit for viruses and a range of xenobiotic agents into the brain and

may initiate neurodegenerative pathology in genetically susceptible individuals.[9]

In addition to the sensory innervation of the olfactory nerve, free nerve endings of the trigeminal nerve (CN V) are distributed throughout the nasal mucosa. The ophthalmic and maxillary divisions of CN V carry information regarding irritation, temperature and pungency. Sensations mediated by non-CN I nerves are those of the 'common chemical sense' and do not encode the qualitative perception of 'odour', *per se*.[10] Although humans possess a rudimentary vomeronasal (Jacobson's organ) pouch at the base of the nasal septum, the elements of this system are vestigial and humans lack an accessory olfactory bulb which would normally receive a projection from this structure. Despite fanfare to the contrary, it is questionable whether humans – indeed mammals in general – communicate by so-called pheromones.[11]

Anatomy of the gustatory system

Taste receptor cells are located within taste buds on the tongue, soft palate, uvula, epiglottis, rostral oesophagus and mucous membranes of the laryngeal cartilages. Most lingual taste buds are found imbedded in the surface of protuberances termed papillae. Fungiform papillae are prevalent on the anterior tongue, circumvallate papillae within the chevron of the posterior tongue, and foliate papillae within the lateral margins of the medial tongue separating the anterior and posterior sectors[12] (Figure 88.2).

The sense of taste is supplied by three cranial nerves: the facial nerve (CN VII), the glossopharyngeal nerve (CN IX), and vagus nerve (CN X). As shown in Figure 88.2, the taste buds on the fungiform papillae are supplied by the chorda tympani branch of CN VII, whereas the taste buds on the other types of taste papillae are supplied by the lingual branch of CN IX. Although it is generally believed that the innervation of CN IX is limited to the posterior third of the tongue, recent studies suggest that it may project afferent fibres beyond this posterior boundary.[13] Taste buds located on the soft palate send their projections centrally via the greater superficial petrosal branch of CN VII and those on the epiglottis, oesophagus and larynx transmit taste information by way of the superior laryngeal branch of CN X. As in the case of olfaction, trigeminal (CN V) free nerve endings, distributed throughout the oral cavity, mediate somatosensory sensations (e.g. pungency, burning, sharpness). All branches of the gustatory nerves enter the brainstem and terminate in the rostral part of the nucleus of the solitary tract. The subsequent projections are not thoroughly understood in humans; however, connections are made with the ventral posteriormedial thalamus and insular cortex. In rodents, fibres from the pons also travel to areas involved in feeding and autonomic regulation,

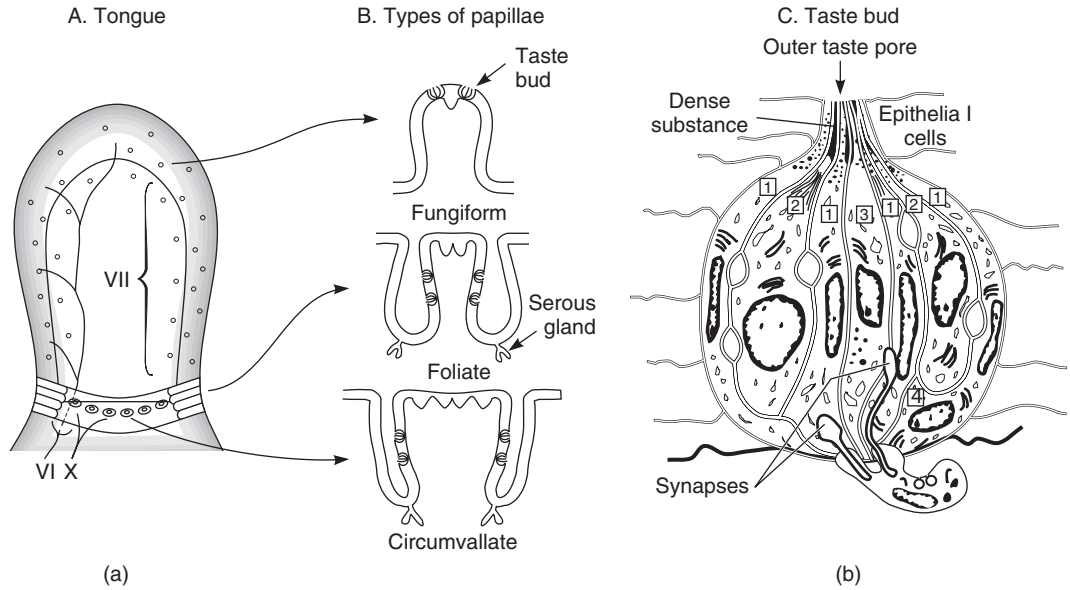

Figure 88.2 (a) and (b) Schematic of the distribution of taste buds on the human tongue. Taste buds of the fungiform and foliate papillae are innervated by CN VII. Those of the circumvallate papillae are innervated by CN IX. CN V carries non-taste somatosensory sensations. See text for details. (c) Schematic of fine structure of taste bud. (1) and (2) are presumably supporting cells that secrete materials into the lumen of the bud; (3) is a sensory receptor cell; and (4) a basal cell from which other cell types arise. Image courtesy of RG Murray, 1973. Copyright RG Murray.

including the lateral hypothalamus, central amygdala and stria terminalis.[14]

Clinical tests of olfactory and gustatory function

The physician of the past assessed the ability to smell by asking a patient to sniff vials containing one or two odorants such as coffee or tobacco, and to report whether or not an odour is perceived. The analogous taste test was to sprinkle grains of sugar or salt onto the tongue, and ask about the corresponding sensations. Unfortunately, such procedures are akin to testing vision by shining a flashlight into the eye, or audition by sounding a bull horn next to the ear. This problem is not corrected, in the case of olfaction, by having the patient attempt to identify the presented odorants, since without cuing even normal subjects have difficulty identifying most odorants. In the case of taste, non-solubilized tastants are often not recognized by patients whose mouths are dry, or who have little time to dissolve the tastants into saliva.

During the last 25 years remarkable progress has been made in the development of reliable, valid and clinically practical olfactory tests. Physicians and insurance carriers are now aware, more than ever, that objective chemosensory assessment is essential for (a) establishing the validity of a patient's complaint, (b) characterizing the specific nature of a chemosensory problem, (c) accurately monitoring medical or surgical interventions, (d) detecting malingering, (e) counselling patients to help cope with their problem, and (f) assigning disability compensation. Importantly, accurate assessment decreases the costs of continuing treatment seeking on the part of patients, who are usually assumed to have a problem even in the absence of objective data.

It should be noted that patients have difficulty ascribing the degree of their olfactory or gustatory dysfunction unless total or near-total loss is apparent. In the case of taste, for example, questionnaire statements such as 'I can detect salt in chips, pretzels, or salted nuts', 'I can detect sourness in vinegar, pickles, or lemon', 'I can detect sweetness in soda, cookies, or ice cream', and 'I can detect bitterness, in coffee, beer, or tonic water' are relatively insensitive in detecting true cases of dysfunction. However, such questions are sensitive in detecting persons without such problems (i.e. they exhibit low positive but high negative predictive value).[15]

Several commercially available tests of olfactory function are now available, including tests of odour detection and identification (for review, see Doty, 2001).[16] The most widely used of these tests (the University of Pennsylvania Smell Identification Test or UPSIT: commercially termed the Smell Identification Test™, Sensonics, Inc., Haddon Hts, NJ) was developed at our centre and evaluates the ability of patients to identify, from sets of four descriptors, each of 40 'scratch and sniff' odorants[2] (Figure 88.3). The number of items correctly identified out of 40 serves as the test score. This measure is compared to norms based upon data from a large number of individuals sampled from the community at large and a percentile rank is determined, depending upon the age and gender of the patient. This test, which correlates strongly with traditional threshold tests, is amenable to self-administration and provides a means for detecting malingering. Commercially available taste tests with high reliability, validity and practicality are now being developed for use by physicians,[17,18] and electrogustometry, which has been available for a number of years, provides quantitative assessments of taste function that are correlated with the number of underlying taste buds.[19]

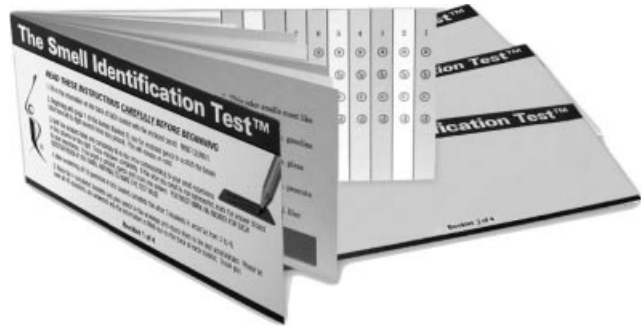

Figure 88.3 The 40-odorant, self-administered, University of Pennsylvania Smell Identification Test (UPSIT). Each page contains a microencapsulated odorant that is released by means of a pencil tip. Answers are marked on the columns on the last page of each booklet. Copyright 2004, Sensonics, Inc., Haddon Heights, NJ 08035.

Traditionally, physicians have assumed that if a patient presenting with the complaint of anosmia fails to report the presence of an irritating vapour via CN V, he or she is malingering. However, this test is not foolproof, as even the most ardent malingerer rarely denies not perceiving a strong irritating substance, particularly one which leads to reflexive mucous secretion or eye watering. Furthermore, trigeminal thresholds to chemicals can be quite variable among individuals. Thus, a more valid means for detecting malingering is to determine the percentage of responses to stimuli that are correct in a forced-choice situation where chance responding can be calculated. When significantly fewer correct responses than expected on the basis of chance responding are demonstrated, malingering is suspected.

Age-related changes in olfactory function

The now well-established age-related decline in olfactory function is exemplified in Figure 88.4.[2] As can be seen in this figure, considerable average decline occurs in the

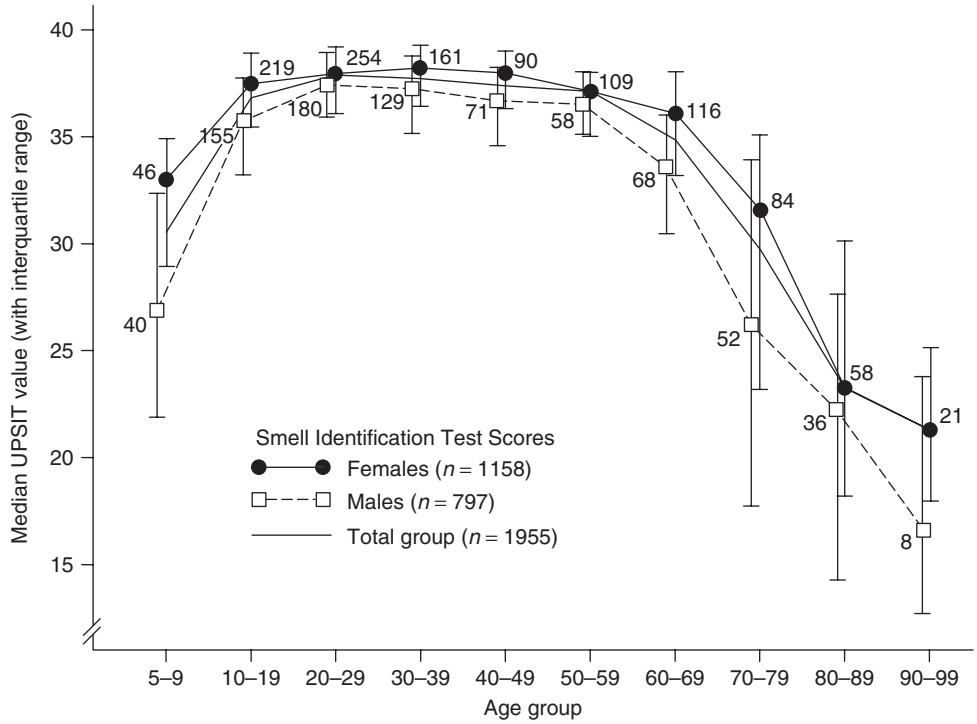

Figure 88.4 Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of age in a large heterogeneous group of subjects. Numbers by data points indicate sample sizes. Reprinted with permission from Doty RL et al., Smell identification ability: changes with age. *Science;***226**:1441–3. Copyright 1984 AAAS.

ability to identify odours in persons after the age of 60 years. In general, olfactory identification ability peaks, for both men and women, during the third to fifth decades of life and significantly declines in the seventh decade. Women outperform men at all ages, with the gender gap increasing in later years.[21]

It is not known to what extent such age-related changes in olfactory function represent the process of ageing, *per se*, or alterations in the chemosensory systems brought about by factors correlated with age (i.e. cumulative viral insults, repeated exposures to environmental agents and air pollutants, alterations in trophic factors, the early progression of neurodegenerative disease pathology, etc.). It is now clear that cumulative exposure to high levels of air pollution significantly alters the ability to smell and may well contribute to neurodegenerative disease pathology.[20] Age-related declines occurs, however, in all cultures, although large individual differences are present, and women, on average, maintain function later in life than men.

Age-related changes in gustatory function

Taste function, like olfactory function, also declines over the lifespan. Older persons show decreased ability to discern sweet, sour, bitter and salty tasting agents, including a number of amino acids at both threshold and suprathreshold levels. Functionally, however, such a decrease has much less impact on the individual than olfactory loss, since whole-mouth tests often show only moderate declines in age-related function.[22] This is due, in part, to the fact that the taste buds in different regions of the mouth are innervated by several different sets of cranial nerves. Such nerves are less susceptible to insult than the fine olfactory filaments. In the case of head trauma, for example, total ageusia, as measured by whole-mouth testing, is rare (<0.5 %), compared to total anosmia.[23] Nevertheless, studies that have tested well-defined localized regions of the tongue to brief presentations of stimuli report marked age-related dysfunction[24] (Figure 88.5). Such losses may be particularly significant for foodstuffs which minimally leach chemicals during mastication.

It is of interest that damage to the chorda tympani nerve, which innervates the anterior tongue, increases the sensitivity of the glossopharyngeal nerve, which innervates more posterior regions of the tongue.[25,26] This phenomenon likely ensures that limited lingual nerve damage does not place an individual at risk from an inability to taste toxic agents, particularly bitter tasting ones. Some dysgeusias seen in the elderly may reflect such release of inhibition.[27] Chorda tympani damage can occur from a number of factors, including

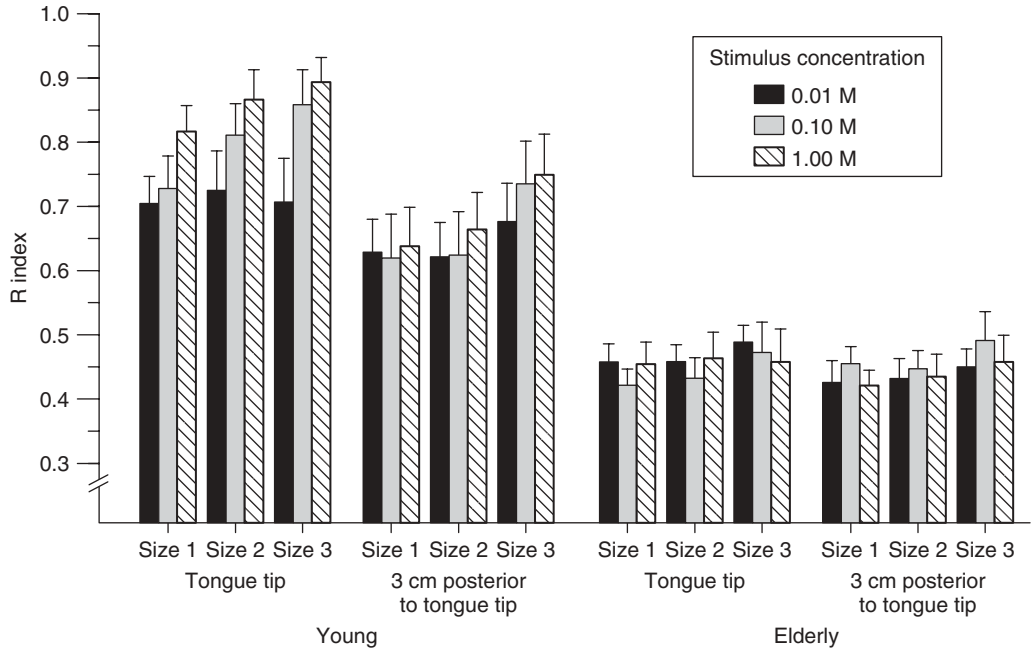

Figure 88.5 Mean (±SEM) sensitivity values (R index) obtained from 12 young and 12 elderly subjects for sodium chloride stimuli presented to the tongue tip and to a medial tongue region 3 cm posterior to the tongue tip for three stimulation areas (12.5, 25, 50 mm^2) and three stimulus concentrations. The sensitivity of the elderly subjects was at near-chance levels and the sensitivity did not increase as either a function of the stimulus area or concentration. Note also that, unlike the case with the young subjects, the tongue tip of the elderly subjects was no more sensitive than the tongue region 3 cm posterior to the tongue tip. Reproduced from Matsuda and Doty,[24] by permission of Oxford University Press.

wisdom tooth removal and ear infections, such as otitis media, experienced early in life.[28]

It is important for the clinician to be aware that complaints of loss of 'taste' usually reflect the loss of flavour sensations derived from retronasal stimulation of the olfactory receptors.[29,23] Thus, other than basic sweet, sour, salty and bitter sensations (or possibly metallic or 'Umami' sensations) or temperature or textural sensations (sharpness, pungency, burning, etc.), the rich experiences attributed to 'taste' are really due to molecules which enter the nose from the oral cavity via the nasal pharynx. Among the hundreds of 'tastes' which are really due to stimulation of CN I are banana, chocolate, strawberry, pizza sauce, vanilla, root beer, cola, liquorice, steak sauce, steak, fried chicken, apples and lemon.

Causes of smell dysfunction in the elderly

The olfactory receptors are rather directly exposed to the outside environment, making them susceptible to insult from bacteria, viruses, toxic agents and other nosogenic stimuli. For this reason, it is not surprising that environmentally induced damage to the olfactory epithelium appears to be the most common cause of age-related decrements in the ability to smell. Indeed, cumulative destruction of the olfactory epithelium occurs over the course of one's life with metaplasia from respiratory-like epithelium appearing as islands within the membrane.[30] However, age-related functional or structural changes may also directly damage the epithelium or predispose it to damage from environmental insults, such as from influenza. Potential changes include reduced protein synthesis or metabolic insufficiency (as in hypothyroidism), changes in the vascular elasticity of the epithelium, altered airway patency, decreased intramucosal blood flow, loss of neurotrophic factors, occlusion of cribriform plate foramina through which the olfactory nerve axons project, increased viscosity of the nasal mucus, atrophy of secretory glands and lymphatics, and, potentially, decreases in enzyme systems that deactivate xenobiotic materials within the olfactory mucosa.[31]

The vast majority of elderly patients complaining of a smell deficit can be classified into one of six proximal aetiologic categories: (i) nasal/paranasal sinus disease; (ii) prior upper respiratory infection (URI); (iii) head trauma; (iv) Alzheimer's disease; (v) Parkinson's disease; or (vi) idiopathic.

Nasal/paranasal sinus disease

Inflammation of the nasal cavity and sinuses (e.g. chronic sinusitis, allergic rhinitis, bacterial rhinitis, viral rhinitis)

reduces upper airway patency, thereby restricting odorant access to the olfactory neuroepithelium. Additionally, structural abnormalities such as marked sepal deviation (particularly with adhesions to the turbinates), polyps and neoplasms can lead to decreased olfactory sensitivity. Even individuals with a moderate degree of ostiomeatal disease, without intranasal polyps, may complain of olfactory loss.[32] The loss of smell can be quite severe in patients with nasal sinus disease, with most being anosmic or profoundly hyposmic. These patients are more likely to describe a gradual onset of olfactory loss than are those patients whose loss is due to prior upper respiratory infections. Fluctuations in smell sensitivity are also characteristic of nasal sinus disease. For example, nasal decongestion from exercise, hot showers or medications may temporarily improve the sense of smell. Administration of corticosteroids (particularly systemic) typically improves smell function in this group of patients and can be used to diagnose olfactory loss due to nasal sinus disease when function is still present. Unfortunately, sustained corticosteroid treatment is not medically indicated in most cases and chronic nasal sinus disease can lead to damage to the olfactory mucosa.[33] Once such damage occurs, olfactory function is not improved by administration of an anti-inflammatory agent. It is encouraging, however, that olfactory dysfunction arising from nasal sinus disease is often amenable to treatment. Management of allergies, sinusitis and structural abnormalities through medication or endoscopic surgery can alleviate smell loss in a number of these patients.

Prior upper respiratory infections

Upper respiratory infections are the most common cause of permanent decreased olfaction in persons older than 50 years.[23] The diagnosis of viral-induced olfactory dysfunction is based upon a history of a viral illness prior to the onset of olfactory loss in combination with the absence of other aetiologic factors. Patients will often describe an olfactory deficit during a 'cold' that was more severe than usual. After recuperation from the illness, however, the sense of smell does not return. These patients are more likely to experience a non-fluctuating hyposmia in comparison with the fluctuating anosmia of patients with nasal sinus disease.

Whether viral-induced smell loss is reflective of the age-related resistance to viral insult or a culmination of repeated insults to the olfactory neuroepithelium (or both) is unknown. Olfactory biopsies in individuals with olfactory dysfunction secondary to tipper respiratory infections demonstrate a decrease in the number of olfactory receptor cells, extensive scarring and islands of metaplasia from respiratory-like epithelium.[5] These characteristics are frequently evidenced in the olfactory epithelium of elderly individuals, suggesting the possibility that cumulative viral insults over time may be one basis for their overall loss, even if a precipitating event cannot be identified or differs from a viral infection.

Currently, no well-established treatments are available for viral-induced chronic anosmia or hyposmia. Nevertheless, there is evidence that some slight improvement occurs over time in approximately half of individuals with this problem, although return to normal function is relatively rare. In one study, for example, 11.31% of anosmic and 23.31% of microsmic patients regained normal age-related function over time.[34]

Head trauma

Most studies have reported incidence rates of smell loss following head trauma between 5 and 15%, although such estimates are not available from random samples of head injury patients at large.[35] Injuries that involve rapid acceleration/deceleration of the brain are most commonly associated with smell loss. Such coup/contrecoup movements lead to shearing or tearing of the olfactory nerve filaments at the level of the cribriform plate. Interestingly, occipital blows are more likely to produce smell loss than frontal blows, presumably because less soft tissue is available for absorbing the impact. It is not presently known whether equivalent head injuries in young and older persons produce equivalent degrees of damage to the olfactory pathways, although it would seem reasonable to expect the elderly to be more susceptible to such loss.

Smell loss in head trauma patients tends to be severe, as most are anosmic rather than hyposmic under objective testing. As with the case of viral-induced smell loss, prognosis depends upon the degree of initial dysfunction, with microsmic patients being more likely than anosmic patients to regain some function over time.[34] In many cases, scar tissue forms at the level of the cribriform plate, blocking entry of axons from regenerating olfactory neurons through the cribriform plate into the central nervous system.

Alzheimer's disease

Most individuals with even mild Alzheimer's disease (AD) demonstrate decreased olfactory function relative to age-matched controls. Physiological changes associated with normal ageing may be responsible, in part, for some of the AD-related olfactory dysfunction. However, even relatively young and early-stage AD patients with mild dementia score markedly lower on olfactory tests than do age-matched controls. Thus, on the 40-item University of Pennsylvania Smell Identification Test, 50% of the items, on average, cannot be identified by early stage AD patients. In a picture identification test analogous to the odour identification test (except that pictures, rather than odours, need to be identified), only 5% of the items are similarly misidentified by the same AD patients.

It now appears that olfactory dysfunction – particularly in conjunction with other risk factors – may be a predictor of subsequent development of AD in older persons.[36–38] In one study, for example, a standardized 12-item odour identification test was administered to 1604 non-demented community-dwelling senior citizens 65 years of age or older.[37] The olfactory test scores were found to be a better predictor of cognitive decline over the following two years than scores on a global cognitive test. Persons who were anosmic and possessed at least one ApoE4 allele exhibited 4.9 times the risk of having cognitive decline than normosmic persons not possessing this allele. This was in contrast to a 1.23 times greater risk for cognitive decline in normosmic individuals possessing at least one such allele. A sex difference was noted. Thus, women who were anosmic and possessed at least one ApoE4 allele were 9.71 times more likely than their normosmic non-allele-possessing counterparts. This corresponding figure for men was 3.18. Women and men who were normosmic and possessed at least one allele were only 1.9 and 0.67 times more likely, respectively, than their normosmic non-allele-possessing counterparts.

Although the olfactory system-related neuropathology of AD may involve the neuroepithelium, most likely central structures are the most heavily involved.[39–43] There is evidence that AD pathology begins in olfactory regions within the medial temporal lobe, most notably layer II of the entorhinal cortex[44,45] and progresses from there to neocortical regions, although involvement of the olfactory bulbs early in the disease process has also been demonstrated.[46,47] A 40% decrease in cross-sectional area of the olfactory tract and a 52% loss of myelinated axons has been reported in AD. Neurofibrillary tangle formation occurs earlier than amyloid deposition within the olfactory bulb of AD patients, and the presence of more than 10 neurofibrillary tangles per olfactory bulb section is associated with a 93.3% AD diagnostic accuracy rate.[41]

Parkinson's disease

Idiopathic Parkinson's disease (PD) is another age-related neurodegenerative disorder characterized by olfactory dysfunction. Interestingly, the proportion of early-stage PD patients with olfactory dysfunction appears to be equal to or greater than the proportion of early-stage PD patients exhibiting a number of the cardinal signs of PD (e.g. tremor). The following general observations have been made: (a) PD-related smell loss is typically bilateral and presents very early in the disease process; (b) the magnitude of olfactory dysfunction is unrelated to disease stage, severity of motor dysfunction or use of antiparkinsonian medications; (c) the olfactory loss is stable over time, even when motor elements of the disease progress; (d) olfactory-evoked potentials are abnormal in PD patients, demonstrating a prolonged latency, or in most cases, an absent response; and (e) among the major motor disorders, the olfactory loss of PD is relatively specific.[48] Thus, decreased ability to smell is absent, or present infrequently or only to a minor degree, in progressive supranuclear palsy (a condition which shares a number of signs with PD), essential tremor, multiple system atrophy, amyotrophic lateral sclerosis, and parkinsonism induced by intravenous administration of the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[49–51]

While the basis for the olfactory deficit in idiopathic PD is unknown, it appears to be indistinguishable from that observed in AD, suggesting the possibility that these two disorders may share a common neuropathological substrate.[52] As with AD, both olfactory vector and degenerative hypotheses could explain the dysfunction. Tangential support for the olfactory vector hypothesis comes from evidence that (a) certain viruses (e.g. encephalitis lethargica) have been epidemiologically associated with PD, (b) a number of xenobiotic agents, including viruses associated with encephalitis, enter the central nervous system via the primary olfactory neurons, and (c) patients whose parkinsonism is due to the intravenous administration of MPTP have relatively normal olfactory function.[9] The possibility exists that the common olfactory alterations observed in AD and PD are secondary to damage to the anterior olfactory nucleus. Thus, intraneuronal pathology related to the protein τ is clearly marked in the anterior olfactory nucleus of neurodegenerative diseases such as AD and PD which are associated with olfactory loss, but nearly absent in such disorders as progressive supranuclear palsy, corticobasal degeneration and frontal temporal dementia, disorders with little or no olfactory dysfunction.[43,53]

Idiopathic factors

A number of individuals presenting with an olfactory complaint lack a clear aetiology for their dysfunction. It is possible that subclinical manifestations of disorders that alter the sense of smell are responsible for some of these cases. For example, we have observed patients presenting to our clinic with complaints of distorted olfactory function of unknown origin who came down with influenza a week or two later. The olfactory losses of a disproportionate number of idiopathic cases occur during the influenza season; thus, some of these cases may reflect influenza that culminates in no other noticeable clinical manifestations.

Causes of taste dysfunction in the elderly

As discussed in detail earlier in this chapter, the subjective complaint of 'taste' loss, a common complaint of the elderly,

is often not verified by whole-mouth taste testing. A number of such patients are undoubtedly confusing 'taste' with 'flavour', and upon careful testing exhibit major olfactory, rather than major gustatory, deficits.[23]

As with olfactory dysfunction, a broad array of age-related changes may predispose the taste system to damage from environmental insults or other factors, including reduced protein synthesis or metabolic insufficiency, changes in epithelial vascularity, decreased blood flow, loss of neurotrophic factors and atrophy of secretory glands and lymphatics.[31] Common conditions seen in the elderly that may interfere with the access of the tastant to the taste bud (transport loss) include inflammatory processes of the oral cavity, bacterial and fungal colonization of the taste pore, and xerostomia. Poor oral hygiene may also contribute to taste dysfunction.

Viral infections, medications and radiation therapy to the oral cavity and pharynx represent the most common causes of sensory gustatory loss. The chorda tympani is particularly susceptible to viral or bacterial insult as it courses through the middle ear. In turn, the middle ear is connected to the Eustachian tube and nasopharynx which provide a portal of entry for infectious agents. Thus, it is not surprising that taste loss or distortion has been associated with upper respiratory and middle ear infections. Numerous drugs have been suggested to alter the ability to taste, including antihypertensives and antilipidemics[54] and drugs affecting cell turnover, such as antineoplastic, antithyroid and antirheumatic agents.[55] Some medications, such as the sleeping agent Lunesta (eszopiclone), produce bitter taste sensations which correlate with their blood and saliva levels.[56]

Neural gustatory loss results from head trauma, neoplasms and a variety of dental and otologic operations that may damage the facial nerve or glossopharyngeal nerve. Injury in this patient population can be to the taste nerves or to more central structures.

In addition to the aforementioned causes of altered taste perception in the elderly, several other conditions are important. Diabetics often experience a loss in taste perception, especially for glucose. This loss can be progressive and eventually extend to other taste stimuli.[57] Burning mouth syndrome is a poorly characterized disorder in which patients describe an intraoral burning sensation that commonly occurs in combination with dysgeusia.[58] This problem is prevalent in postmenopausal women. Although no clear aetiologic factor has been identified, hormone replacement and tricyclic antidepressants are reportedly effective in alleviating the oral sensations in some cases. The degree to which neurological diseases such as Alzheimer's disease influence taste function is currently under study.

Evaluating and managing elderly patients with chemosensory dysfunction

In general, a thorough medical history will identify the proximal cause of most smell and taste problems. During this history, the clinician should question the patient as to whether there is loss (e.g. anosmia) or a decrease (e.g. hyposmia) in function and whether the symptoms are unchanging, progressive or fluctuant. The degree to which the loss or distortion is localized to one nostril or the other, or to one section of the tongue or the other, is useful in establishing whether a given nerve is involved. Antecedent events (i.e. prior upper respiratory infection, head trauma, medications, surgery) leading up to the dysfunction as well as the duration of symptoms are important pieces of information to be gathered from the history. For example, fluctuating olfactory deficits suggest interference with the transport of the odorant to the olfactory neuroepithelium (e.g. nasal sinus disease) rather than a sensorineural disorder.

After obtaining a thorough medical history, it is critical to evaluate the patient objectively, so as to characterize the nature of the dysfunction. In most cases, olfactory dysfunction is the problem. Thus, even when the patient reports that smell is all right and that taste is problematic, quantitative olfactory testing should be performed. If unilateral dysfunction is suspected, the olfactory test can be administered to each half of the nose separately while occluding the contralateral naris using a piece of Microfoam^{TM} tape (3M Corporation, Minneapolis, MN). Contemporaneously, a thorough upper airway examination, ideally using endoscopic procedures, should be performed along with appropriate imaging of the sinuses and higher brain structures. If nasal or intracranial disease is found, appropriate medical or surgical treatment should be initiated, and olfactory testing should be repeated some time after the completion of the treatment regimen to ascertain if improvement has occurred. Obviously, the basic diseases associated with ageing should be ruled out by the physician to preclude their possible association with the chemosensory dysfunction. Importantly, a review of the medications taken by the elderly should be undertaken, particularly if dysgeusia is the presenting symptom.

If the medical tests prove negative, it is likely that the dysfunction is due to neural damage for which no treatment is available (e.g. damage to the olfactory receptors proper). In this case, it is still prudent to assess the chemosensory function quantitatively and obtain a percentile score for the patient. While an older person may evidence, in an absolute sense, considerable olfactory loss, it is still important to characterize this person relative to his or her peer group. Thus, an 85-year-old man may have olfactory loss indicative of marked hyposmia; however, he may still be at the 75th percentile of his normative group, indicating that he is

outperforming three-quarters of his peers. Simply telling him this fact is highly therapeutic as elderly persons expect some degree of decline in their function, but appreciate it when their decline is still not as great as that seen in most of their peers. This simple rule is very beneficial and ensures that at least half the patients complaining of chemosensory function can receive meaningful psychological benefit.

In cases where borderline dysfunction is present in menopausal women, the astute clinician can explore whether or not hormone or vitamin replacement therapy may be indicated in an attempt to return function. This is particularly the case in burning mouth syndrome, where such treatments have been found effective in some cases.[59] Although zinc therapy has been suggested in the literature, double-blind studies indicate that zinc is no more effective than placebo in helping patients with chemosensory disorders (unless, of course, frank zinc deficiency is present).[60] One study reporting effectiveness of the antioxidant α-lipoic acid had no controls and the number reporting resolution was of the same magnitude as would be expected from spontaneous resolution.[61] Some cases of taste dysfunction may represent age-related xerostomia, and therefore this condition should be addressed and, if present, treated as well as possible.

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Key points

- Taste and smell are critical for determining the flavour of foods and beverages and for protection from leaking natural gas, fire, toxic agents, and spoiled beverages and foodstuffs.
- Smell dysfunction is the norm, not the exception, for persons over the age of 65 years.
- It is important for the physician and patient to have an accurate understanding of a patient's abilities to taste and smell, and sample quantitative tests of smell function are widely available.
- Smell loss is among the very earliest signs of Alzheimer's disease and idiopathic Parkinson's disease.
- The most common cause of *permanent* smell loss in the elderly is an upper respiratory infection.
- Some recovery can occur spontaneously over time. Factors that determine prognosis include age, time since onset of problem, and degree of dysfunction, with the latter being most important.

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SECTION 9

Bone and Joint Health

CHAPTER 89

Paget's disease of bone

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Introduction

Sir James Paget described the disease that bears his name as *osteitis deformans* in a series of monographs published in the latter half of the nineteenth century.[1] At this time, we understand much more about the disease, including how to treat it, but its aetiology remains uncertain, perhaps even mysterious.

Paget's disease occurs in monostotic or polyostotic forms. The monostotic form occurs in a single bone, most frequently in a small quarter to half-dollar size lesion in the pelvis or lumbar spine. The pathologic description given below describes both monostotic and polyostotic Paget's disease. Monostotic Paget's disease is usually asymptomatic, although unusual placement of monostotic disease in the higher vertebrae, for example, with pathologic fracture can become symptomatic. Polyostotic Paget's disease is generally described as involving more than one bone. It is worth noting that monostotic disease of a long bone, the femur for example, behaves more like polyostotic disease than monostotic disease, even if only one bone is involved. The rest of the presentation will describe polyostotic Paget's disease unless otherwise noted.

Pathology of Paget's disease

Microscopic

Pathology at the cellular level is frequently divided into three types that correspond to early, middle and late stages of Paget's disease (Table 89.1). These may all be found in a single bone, proceeding in an orderly manner from early to late.[2] The early descriptions of the stages were generally called osteoclastic (early), osteoblastic (mid) and mixed (late). One could occasionally run across a very late stage of the mixed phase that was described as 'burned out'. More modern descriptions combine the osteoblastic and mixed phases to one and include the 'burned-out' phase as the third. The early stage corresponds to increased osteoclastic activity without compensatory increase in osteoblastic activity. Examination of such areas of pagetic bone demonstrate large osteoclasts, frequently several times bigger than normal osteoclasts. All osteoclasts appear to have multiple nuclei, perhaps in the range of four to eight, but pagetic osteoclasts frequently have 20 to 40 nuclei. In the second phase (Table 89.1) osteoblastic activity in the area appears to be dramatically increased, but severely disorganized. Routine findings include disorganized matrix, woven bone and occasional areas of malacic or non-mineralizing osteoid. The characteristic order and architecture of cortical bone is lost and the cortical-trabecular boundary is lost. In this phase, both osteoclastic and osteoblastic activity is increased. Finally, in the 'burned-out' phase, activity of the pagetic bone appears to have returned to about normal, but the abnormal architecture remains. Most monostotic Paget's is found in either phase two (mixed) or in the 'burned-out' form. In the third phase the abnormal architecture remains despite the relative normalization of cellular activity. Normal bone in the same individual, from another skeletal site or from an uninvolved portion of the pagetic bone, appears perfectly normal. It has appropriately sized osteoclasts with normal activity as well as normal osteoblasts and osteoblastic activity.[3] This appears to be true even for areas that might be expected at some later date to become pagetic.

Macroscopic

Pagetic bone is larger than normal bone, but significantly weaker. The bone appears 'coarse' rather than with the smooth surface of normal bone. Although the origin of the bone remains recognizable, it is frequently misshapen or bent, virtually always in weight-bearing long bones. The bone is hypervascular and may have multiple arteriovenous shunts.[4] Paget's disease is one reported cause of high output congestive heart failure.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 89.1 Phases of Paget's disease.

Phase	Bone morphology	Activity
Osteoclastic	Normal, but increased osteoclastic size and activity	Osteoclast
Mixed	Changes of osteoclastic phase plus great increases in osteoblastic activity, poorly mineralized or osteomalacic bone, woven bone, large seams of osteoid, loss of cortical trabecular interface	Osteoclast and Osteoblast
Burned out	Activity returning to normal but may still appear somewhat increased	Osteoclast and Osteoblast

Pagetic involvement of bones occurs idiosyncratically within very specific parameters. Large bones are much more likely to be involved than small bones. Anyone who has treated multiple cases of Paget's will have seen some unusual small bone involvement in wrist, hand or foot, for example. A list of bones frequently involved is shown in Table 89.2. Involvement in long bones generally starts at one end and proceeds toward the other end over a period of years. The disease does not cross joint spaces for long bones. Similarly, involvement in the pelvis or skull begins at one location and gradually extends across the entire bone. Unlike long bones, Paget's disease does frequently seem to spread across sutures in the bones of the skull or pelvis. Involvement of one long bone, the left femur for example, does not determine the involvement of the other, in this example the right femur. Usually, it is not involved, but occasionally it is.

The sequelae of Paget's disease may generally be inferred from the observations of micro- and macroscopic changes in bone. Changes in measures of osteoclastic activity either in serum or urine occur first and remain elevated. Urinary hydroxyproline was the measurement first used, but required specific dietary restrictions to avoid gelatine and gelatine-containing foods to be used accurately. Serum acid phosphatase, a potential serum marker of osteoclast activity, was occasionally used in some studies, but suffered from a series of difficulties. It was only elevated in about 20% of cases of Paget's and was also a marker for prostatic disease, a fairly common finding in many male patients with Paget's. More recent measures of bone-specific collagen breakdown markers in serum or urine have obviated these difficulties. These markers include N-telopeptide and pyridinium cross-links and provide much better estimates of osteoclastic activity. Urine studies should always be accompanied by a measurement of urinary creatinine to ensure comparability of one specimen to the next. These measures are routinely elevated in all phases of Paget's disease.[5] Measures of osteoblastic activity, primarily in serum, are also routinely elevated in Paget's disease. Older measures of this activity include serum alkaline phosphatase and the heat-stable fraction of the serum alkaline phosphatase. Although the first measure is routinely available in chemistry panels, it is not terribly specific. The heat-stable fraction is more specific, but is relatively difficult to do. It is still not entirely specific for bone alkaline phosphatase as opposed to the enzyme from other sites. Additional tests assays of osteoblastic function including bone-specific alkaline phosphatase and other markers like osteocalcin are now available They are not reported to be as sensitive a marker for Paget's disease as the older assays despite the fact they are generally considered to be more specific.[6] Radiological changes can be seen from the earliest (osteoclastic) stages of the disease on both plain films and radionuclide scans. On plain films, the early lesions appear as lucencies. Depending on the site they frequently have specific names. The most common of these include 'osteoporosis circumscripta'. This describes an early lesion in the skull that appears as a circular lucency on plain film of the skull. Similarly, the 'blade of grass' lesion describes a chevron-shaped lucency in a long bone. Over time (years), this lesion may be observed to march down the length of the bone at an approximate rate of one centimetre per year followed by signs of the osteoblastic/mixed stages of the disease.[7] These signs include enlargement of the bone, irregular calcification and loss of the cortical trabecular demarcation in bone. Radionuclide scans of bone will also show significant changes. Affected areas are hot. In long bones or other large bones, clear demarcation can be seen between affected and unaffected. All of these radiological findings are generally considered pathognomonic for Paget's disease except that 'osteoporosis circumscripta' needs to be clearly delineated

Table 89.2 Bones commonly affected by Paget.

- Pelvis
- Femur
- Tibia
- Skull
- Vertebrae
- Clavicle

from the 'punched out' lesions observed in the skull with multiple myeloma. Further, very occasionally, lesions of the lower lumbar vertebra may be impossible to differentiate from metastatic (prostate) carcinoma without biopsy. Magnetic resonance imaging (MRI) has been a major boon in this regard, however.[8]

Sequelae of Paget's disease

Most of the sequelae of Paget's disease can be inferred from the knowledge of its effect on bone, that is the bone becomes larger, but weaker. The major exception to this is the most feared complication of Paget's disease, osteosarcoma. This tumour is a rare but deadly outcome arising from pagetic bone, usually decades after it was first affected. Estimates of its frequency are quite low perhaps 1–3% of individuals with Paget's disease.[9] Mortality in affected individuals is quite high, in some series 100%, even after the development of successful protocols for the treatment of childhood osteosarcomas. The reasons for the abysmal outcomes in osteosarcomas related to Paget's are at least twofold. First, the central location of Paget's disease prevents the common first-step treatment, excision/amputation. Secondly, the symptoms of osteosarcoma are very non-specific and therefore frequently missed. The major presenting complaint is a significant worsening of Paget's symptoms, particularly bone pain. Bone pain waxes and wanes spontaneously throughout the course of Paget's disease. After many years or decades of such spontaneous changes, patients frequently do not complain of them to their physicians until it has been present for several months. In this setting, the osteosarcoma has frequently progressed too far for successful treatment upon its initial discovery.

A second feared complication of Paget's is probably more unusual, platybasia, or basilar invagination. Individuals with severe Paget's disease of the skull will be noted to have a 'sharpening' or 'lipping' of the occiput on lateral skull films. Instead of the normal curve of the occiput noted on lateral film, the bone begins to protrude downwards or 'lip'. This is a radiological sign of a falling down of the skull around the spinal column. Essentially, the skull is too weak to hold its own weight and over a period of time it will collapse while the falxes hold the brain in place. This circumstance will cause hydrocephalus and eventual herniation of brain with death. This process extends over years. Neurosurgical intervention for the hydrocephalus can maintain normal pressure.[10]

Congestive heart failure is a reported complication of Paget's disease. Arteriovenous shunting of blood through affected bone is reported to produce high output congestive heart failure in individuals with more than 15% of their skeleton involved by the disease. Even in very active polyostotic Paget's disease, this complication is very rare in my experience and is only included for completeness and because the causes of high output failure are so limited. Urgent treatment to limit the activity of the pagetic bone is recommended. This reduces the arteriovenous shunting and decreases the need for the high output state. Altered blood supply ('steal syndrome') is suspected or reported in individuals with Paget's disease of the skull who complain of somnolence. Similarly, this 'steal syndrome' has been implicated in an individual with Paget's of a vertebra and paralysis below that level.[4,11]

Other complications are more common, but generally less severe. Fracture through weaker pagetic bone is relatively common. Considerable excess blood loss may occur because of the vastly increased vascularity of pagetic bone. Longitudinal fractures or fissures are described. Bowing of affected weight-bearing long bones is an integral part of the disease and is associated with gait abnormalities and/or unsteadiness, osteoarthritis in nearby or adjacent joints and in painful microfractures that occur in severely bowed lower extremities. Some of these microfractures extend through the bone and become full-blown displaced fractures. Such microfractures occur when weight placed on the bowed extremity increases the curvature (circumference) of the bone, stretching the bone beyond its endurance. Treatment of this type of fracture requires either bracing or osteotomy to straighten the bone in order to heal and prevent further fractures in that bone. In the case of osteotomy, patients should be treated prior to surgery to reduce the vascularity of the affected bone.

Any place a nerve passes through a bony foramen or through bone, the potential exists for Paget's disease to narrow the channel and impinge upon the nerve, causing pain and/or eventually loss of the nerve function.[12] The most common of these is probably seen in Paget's of the skull where approximately 70% of patients are reported to have mixed sensineural hearing loss. Other nerves pass through foramen in the skull. Blindness is an unusual but reported complication also. Facial nerve palsies can also be observed. Hypercementosis in teeth, an idiopathic condition of increased accretion of bone on one or more roots, causing tooth pain has also been reported in individuals with Paget's of the skull.[13]

Similar nerve palsies may be observed in effected peripheral locations. Certainly the most severe of these may be related to weakness/fracture, as is the case in (partial) spinal cord transaction related to thoracic or cervical vertebra collapse due to pagetic involvement. Spinal stenosis, related to involvement of one or more vertebra with Paget's resulting in critical narrowing of the spinal canal has also been reported, but is thought to be less common than the steal syndrome.[10,12]

A final important sequelae relates to the ongoing extended and accelerated bone resorption and formation. Paget's disease of the pelvis in an individual after hip

replacement can result in an unstable position for the acetabulum, which over a period of years can move a significant distance. Similarly, Paget's disease of the skull or mandible can result in tooth migration. In the cases in which this was reported, dentures required constant attention over a period of years to ensure comfort and adequate mastication.

For the patient, aside from the unusual catastrophic sequelae, Paget's disease represents an almost constant chronic irritation. The symptoms of the disease are limited, but the symptoms of the sequelae have an almost constant effect depending on the bone(s) affected: arthritic complaints in the joints most nearly related to the affected bone are constant; partial deafness in individuals with Paget's of the skull; gait abnormalities and pain in individuals with long bone involvement. Many of these may be at least partially ameliorated by the use of braces, shoe lifts and other orthotic devices.[14]

Presentation of Paget's disease

Patient's with Paget's disease generally present in one of three ways. First, individuals discovered on a routine blood test with an alkaline phosphatase elevated several times above normal. While other obvious sources of pathology would need to be ruled out, the evaluation should include a more specific measure of osteoblast activity as described above, a serum bone specific alkaline phosphatase or osteocalcin. Measures of osteoclastic activity like N-telopeptide or pyridinium cross-links in serum or urine would be appropriate if readily available, but not necessary. If the serum alkaline phosphatase is elevated due to Paget's disease, one would expect that measures of osteoclast activity would surely also be elevated. If these measures were elevated more than 50%, then the next step would be to perform a radionuclide scan of bone and obtain X-rays of hot spots. If these tests showed an individual with Paget's disease outside of the lumbar spine or pelvis (that is a patient with polyostotic rather than monostotic disease) appropriate treatment would then be undertaken. Individuals with apparent monostotic Paget's disease in the pelvis should followed longitudinally over a period of years to make sure the Paget's disease is not extending.

The second major group will present either with chronic bone pain or deformity. In this group, pain may have been present for years, and the deformity has usually been slowly worsening. On physical exam, the indicated area is usually warm and erythematous, but not painful. It is without nodes or other indications of infection. The patient may have complaints specific to the pagetic involvement, loss of hearing and headaches for Paget's of the skull. They may have arthralgias as well as bone pain around the involved bone, or occasionally some distance from it. The laboratory evaluation for this patient should include the tests described above: a test of osteoblastic activity, a bone-specific alkaline phosphatase or osteocalcin, but again, not necessarily a measure of osteoclast activity. If these are elevated then the patient should get a radionuclide scan with X-rays of the hot spots. Pain suggesting microfracture or stress fracture should probably prompt referral to an orthopaedist for appropriate follow-up.

The third major group will be individuals who present with an established diagnosis. In these cases, review of the patient's record should demonstrate a radionuclide scan with appropriate X-rays of 'hot spots', serial serum measures of osteoblastic activity over the course of treatment and non-treatment intervals and finally appropriate follow-up exams, for example audiology evaluations in patients with Paget's disease of the skull or appropriate gait evaluations for individuals with lower limb involvement of their disease. Appropriate follow-up radionuclide scans should probably not be performed more frequently than annually, unless new or changed symptoms appear.

Epidemiology of Paget's disease

Autopsy series suggest a prevalence rate of about 4% for Paget's disease in individuals over the age of 40 years and about 7% for individuals over the age of 70 years.[2,12] The disease increases in prevalence with age. These numbers include both individuals with monostotic and polyostotic Paget's disease. It is generally thought that polyostotic disease makes up 5% or less of the combined numbers and is probably less common than that in the younger age group. The other caveat that needs to be considered in estimating the number of individuals with Paget's is the ethnic origin of the population. This factor plays a large role in the frequency of Paget's disease. Individuals of European descent, particularly northern Europe, excluding Scandinavia, are particularly likely to get Paget's disease.[15,16] Individuals of southern European descent are less likely, but the risk is still appreciable. Native African and Asian peoples have miniscule prevalence of Paget's disease. On the other hand, African-Americans are clearly noted to get Paget's disease. Thus the origin of the population studied determines in part the prevalence of Paget's disease.

Men are slightly more likely to get Paget's disease than women with a ratio that approximates three to two. Since the absolute number of women in the general population is about double that of men over the age of 65, the relative risk for Paget's disease is probably about three times greater in men.

Aetiology of Paget's disease

Even at this relatively late date, the aetiology of Paget's disease of bone remains somewhat obscure. There is a clearly positive family history in about 10–50% of patients with

Paget's disease of bone.[17] The effect of this observation is blunted by the fact that in everyday practice, the individuals affected seem most frequently to be cousins or uncles. Occasionally, the relationship is even more obscure. Two of the most severely affected individuals I have ever seen were related – as sisters-in-law. It seems relatively unusual for siblings to be involved or for a parent and child to be involved. As a measure of the rarity of this effect, there are reports of multiple generational involvements in several kindreds, but good documentation of the effect even recently is still reportable. Some of this effect can probably be accounted for by the relatively late onset of the disease. At the time a patient presents with Paget's, frequently his or her parents and their siblings will be unavailable for examination and their own children may still be years away from the potential to develop the disease. There is about a 15% chance of acquiring Paget's disease in one's lifetime if a first-degree relative has that diagnosis. Recent studies have reported genes associated with Paget's. The database, *Online Mendelian Inheritance in Man*, lists Paget's disease as a heritable trait with four different loci on three separate chromosomes being linked to Paget's (as of this writing).[18–22]

Despite the recognition of vertical transmission of Paget's within kindreds, several investigators believe that the disease is transmitted by a slow virus. They point to the fact that the disease is distributed in relatively temperate climates, as one might expect of a virus. Viruses, measles for example, cause giant cell formation (in the pneumonic form) that resembles the pagetic osteoclast. Lastly investigators have reported viral like particles in these pagetic osteoclasts using electron microscopy. There is some disagreement about which virus it is, but respiratory syncytial, canine distemper and paramyxo viruses have all been reported to be associated with it.[23–25] Recent reports have discounted the evidence for involvement of measles specifically, and a separate report has suggested that the evidence for virus particles in osteoclasts previously reported may be related to contamination, rather than as a causative agent.[26]

One potential issue that remains to be resolved is whether or not all Paget's disease is the same and therefore has the same aetiology. In particular, descriptions of Paget's disease in several generations frequently sound unlike the usual type of Paget's disease. Thus, kindreds are described with multiple recurrent fractures through clastic lesions in appendicular bone resulting in limb amputations in multiple members of the kindred. It is clear that the description falls in the range of Paget's disease and it would be difficult to call it anything else. Still, this is a very unusual outcome for the disease. These observations implicitly raise the question of whether or not *osteitis deformans* is a 'final common pathway for a series of diseases of hyperactive osteoclasts or a single specific disease'. In that vein, Paget's disease of bone has a series of puzzling qualities, which seem to make the latter possibility more likely. The frequent presence of the disease in large bones, rather than small bones, as well as the local presence of the disease in one femur rather than both, or one humerus rather than both would be hard to understand if a genetic defect were the cause, since all the bones would be affected. An infectious process would be easier to understand, since these are usually localized by definition. Recent reports suggest that a combination of genetic and infectious (viral) aetiologies combine to produce Paget's disease[18,27] working via disturbances in osteoclast and osteoblast physiology. This hypothesis suggests abnormalities even in normal bone, but still does not explain the observed self-limitations of the disease to pagetic versus non-pagetic bone.

In summary, the aetiology of Paget's disease is not conclusively known. Good evidence exists for both a viral and a genetic basis for the condition, although the specifics of how either would produce the syndrome observed remains uncertain.

Treatment of Paget's disease

The aims of treatment of Paget's disease of bone must be to decrease the deformities of bone and reduce the rate of fractures induced by the disease. Controlling the disease should, by definition control the risk for sequelae. That said, there is no evidence-based report of any drug decreasing deformities or reducing fractures in Paget's disease in a double-blind, placebo-controlled trial. On the other hand, decreasing the cellular activity of pagetic bone should limit all of the sequelae of the disease. Multiple drugs in multiple trials have been shown to decrease the activity of pagetic bone.

The earliest successful treatments of Paget's disease used calcitonin (Table 89.3). Calcitonin is a peptide hormone secreted from the thyroid. Thyroid tissue was readily available from slaughter houses to be extracted. Calcitonin acts directly on osteoclasts via receptors to decrease cellular activity. Its effect in man appears to be limited. Individuals with clear cell thyroid carcinoma may have levels of serum calcitonin of a magnitude higher than normal without apparent abnormalities of mineral metabolism. Fowl and fish calcitonins appear to be several times more potent than human calcitonin. In egg-laying animals, serum calcium rises in order to provide calcium to the egg. Osteoclast activity rises in order to mobilize this calcium from the skeleton. When the eggs require less calcium, calcitonin is secreted, osteoclastic activity declines rapidly, and the serum calcium returns to normal. The rationale for the use of calcitonin for the treatment of Paget's disease of bone is readily apparent. The earliest available calcitonin in wide usage was salmon calcitonin given by daily injection. It reduced serum alkaline phosphatase by about 40% within six months. The side effects were limited to local reaction at

Table 89.3 Calcitonin.

- Only injectable is approved
- Side effects – nausea in about 20%
- Flushing occasionally
- Not as powerful as bisphosphonates
- Useful only for people who cannot take bisphosphonates
- Tachyphylaxis develops within six months
- Dosage 50 or 100 IU daily or thrice weekly for 6–18 months can be reported after a rest period – usually at least three months

the injection site, about 20% of patients complained about flushing after the injection and about 20% complained of nausea. The injection was usually given immediately before retiring to avoid or minimize these complaints. Of more concern, however, was tachyphylaxis. By about six months, virtually all patients had reached the maximum benefit to be achieved from therapy. Stopping therapy for some period of time (3–6 months) then restored some additional sensitivity to the drug, but usually also allowed some escape from the drug during the rest period. The end result is that some resistance to therapy appears to supervene over a period of years. Lastly, it needs to be noted that although inhaled calcitonin has been approved for osteoporosis therapy, the FDA has only approved injectable salmon calcitonin for therapy of Paget's disease. Injectable calcitonin remains in limited use for treatment of Paget's disease.[28]

At about this time, an early bisphosphonate, etidronate also became available for use in treatment of Paget's disease (Table 89.4). Bisphosphonates block osteoclastic activity and in the case of etidronate and several other early variations of the class also interfere with osteoblastic activity. All oral forms of the drug are remarkably poorly absorbed. They require strict adherence to protocol for adequate absorption, usually first thing in the morning (i.e. nil per os (NPO)) taken only with 6–8 oz of water and nothing else by mouth for an extended period, usually about an hour. Still in its day, etidronate provided a relatively good response with serum alkaline phosphatase falling about 50% from pretreatment levels. The drug could only be used for six months at a time; it then required a 'rest period' of about 3–6 months. Failure to permit this rest period can be followed by symptomatic osteomalacia.[2,12,29] Newer bisphosphonates have generally supplanted etidronate for therapy of Paget's disease.

Table 89.4 Bisphosphonates.

Agent	Route	Dose and frequency
Etidronate	Oral	200 or 400 mg daily for 6 mos. May repeat after 6 mos. Rest between repetitions imperative
Alendronate	Oral	40 mg daily for 6 mos. May repeat if necessary
Risedronate	Oral	30 mg daily for 2 mos
Pamidronate	IV	30 mg over 4 hrs for 3 days or 60 mg over 4 hrs daily twice
Zoledronic acid	IV	5 mg over 15 min. Repeat after two years if necessary

The newer oral bisphosphonates, alendronate, risedronate, ibandronate and the injectable forms, pamidronate and zoledronic acid (Table 89.4) appear to target only the osteoclast. They are much more successful in reducing osteoclastic and therefore osteoblastic activity than the older drugs.[30–33] These drugs permit reduction of alkaline phosphatase to the normal range in about 80% of cases. There are a few open-label head-to-head trials in series that permit some stratification of effect. Thus, pamidronate probably works less well than the others and zoledronate may work best. Pamidronate and zoledronate are probably the most convenient in that they only require infusion over a relatively short period of time. Further, patient compliance is assured. They may be repeated if necessary. The oral forms are used for relatively short periods of time and may also be repeated if necessary. These therapies will reduce osteoclastic/osteoblastic activity to normal in most cases, although more than one round of therapy may be needed.

Non-prescription and non-pharmacological therapy

Individuals taking bisphosphonates should always assure adequate calcium intake. This will probably necessitate calcium supplementation. Depending on dietary intake, most patients will need an additional 1200 mg of supplemental calcium. Adequate vitamin D intake should be assured also. We routinely give 1000 IU per day to our patients with or without Paget's disease. The aim would be to maintain a serum vitamin D measure more than 35 ng dl^{-1}. To treat bone pain, arthralgia, or arthritis, non-steroidal anti-inflammatory agents are recommended.

Indications for treatment

The major indications for therapy are to ameliorate symptoms related to Paget's disease, including bone pain and headache. Most physicians would also like to prevent the sequelae, including nerve entrapment, bowing of weight bearing extremities and fractures. As mentioned previously, there is no double-blind, placebo-controlled study that demonstrates that this is possible, but it seems likely that reducing the effect of Paget's at a cellular level would have this outcome. 'Burned-out' disease or previously treated disease, notable for relatively normal serum studies

of osteoblastic activity despite obvious bony abnormalities on X-ray or bone scan should be followed. All patients should have non-pharmacological interventions described above offered to them. Individuals with Paget's disease and renal disease should be treated with injectable salmon calcitonin rather than bisphosphonates.

Follow-up studies after treatment with injectable bisphosphonates are appropriate within weeks of the treatment and as the physician deems appropriate until the next date of potential treatment. Individuals whose serum tests normalize should be followed until their tests begin to rise or symptoms recur at which time therapy can be considered again (see below). Since oral bisphosphonates take longer to act, follow-up intervals may be spaced further apart. We tend to use an interval of 4–6 weeks for the first visit. At that visit it is important to ensure the patient is taking the drug as prescribed. Further visits usually occur at three and six months from the time the drug was started. The drug must be stopped by six months. Follow-up visits then occur at three-month intervals until the next date for available therapy, unless the patient's osteoblastic markers have normalized. In this case, we would move the follow-up visits out to about 4–6 months until evidence of disease reactivation recurred as described above. We would then treat again.

Final considerations in Paget's disease

In individuals without metabolic bone disease, bone turnover occurs slowly, such that the half-life of skeletal calcium is estimated to be about 10 years. In areas of active Paget's disease, the half-life of skeletal calcium is estimated to be about six months. This stark difference may be responsible for the reported increased incidence of hypercalcaemia or primary hyperparathyroidism reported with Paget's disease. In the older literature, the incidence of primary hyperparathyroidism was reported to be as high as 15%. On the other hand, much of this data was obtained prior to our present understanding of the inverse relationship between serum 25-hydroxyvitamin D and parathyroid hormone. Individuals with low serum 25-hydroxyvitamin D, high serum calcium and elevated parathyroid hormone can return serum calcium concentrations toward normal or into the normal range with appropriate vitamin D supplementation. The recommended dosage and duration of supplementation is the subject of some debate now, but raising serum vitamin D levels into the lower end of normal range should be adequate for this effect. This can probably be accomplished with a supplement of 1000 IU of vitamin D per day. It must also be remembered that the increased activity of the pagetic bone is releasing more calcium from the skeleton into serum. This calcium should suppress parathyroid hormone release. Finally, individuals lose renal function as they age and when enough renal function is lost, serum parathyroid hormone levels begin to rise. Patients with age-related (or unrelated) renal impairment with secondary hyperparathyroidism who develop Paget's disease (or in whom it progresses significantly) may then present with hypercalcaemia with elevated or not completely suppressed serum parathyroid hormone levels. These factors should be kept in mind when evaluating a patient with Paget's disease and hypercalcaemia.

The second issue to be considered is related to this first issue. The question of normal bone in Paget's disease has intrigued investigators for years. The majority of bone in a patient with Paget's disease is normal, at least as far as we can tell. Treating the pagetic bone necessarily exposes the normal bone to the same treatment. Therapies for Paget's are frequently used to treat normal (but osteoporotic bone), but the doses are usually greatly increased. In the old days, using etidronate (an early bisphosphonate) required a drug holiday of usually six months after six months of therapy to avoid the development of osteomalacia in normal bone. The newer bisphosphonates that are more osteoclastic specific should not require (as much) drug holiday. A potential cloud on this horizon, however, relates to recent reports of osteonecrosis or minimal trauma non-osteoporotic fracture after prolonged use of these bisphosphonates. The risk for developing this complication is about 5 in 10 000, when the drugs are used at 'osteoporotic' dosages, not at the higher doses used in Paget's disease. It is likely that bisphosphonates preferentially locate to the active bone of Paget's disease and initially the normal bone is relatively spared. As successful treatment progresses, however, the pagetic bone will become less active and the exposure to normal bone should become correspondingly greater. This type of fracture with minimal trauma or osteonecrosis in Paget's, have been associated.[34] This is certainly not a reason to not treat Paget's disease. It is a reason to carefully consider how long and how aggressively to continue to treat Paget's disease.

The last presently unanswered question about Paget's relates to recently reported declines in prevalence of the disease in areas where it was once greater.[35] These observations will have to be integrated with the theories of genetic versus (or combined with) viral aetiologies.

Key points

- Paget's disease produces large but weak bone.
- Paget's disease can develop into osteosarcoma.
- Side effects include platybasia, heart failure, deafness, fractures and deformity.
- Bisphosphonates are the treatment of choice for Paget's disease.

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CHAPTER 90

Management of osteoporosis; its consequences: a major threat to quality of life

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Introduction

Osteoporosis is a skeletal disorder, characterized by compromised bone strength, predisposing a person to an increased risk of fracture. The major fragility fractures are those of the forearm, vertebral body and hip, but fractures of the humerus, pelvis and tibia are not uncommon in patients with osteoporosis. Fragility fractures are a major cause of excess mortality, substantial morbidity and health and social service expenditure in older people.[1] It is therefore important that effective strategies are developed and implemented to prevent these fractures.

Epidemiology of osteoporosis and fractures

The World Health Organization (WHO) has quantitatively defined osteoporosis as a bone mineral density (BMD) 2.5 standard deviations or more below the mean value for young adults (T-Score ≤ -2.5).[2] The prevalence of osteoporosis at the hip increases in women from 8% in the seventh decade of life to 47.5% in the ninth decade. The incidence of fragility fractures also increases with advancing age, but is higher in women than men. The majority of these fractures occur in people above the age of 75 years, with a three- to fourfold higher rate in institutionalized older people than community-dwelling individuals of the same age. The lifetime risk of fragility fractures for a 50-year-old woman in the UK is 53.2%, compared with 20.7% for a 50-year-old man.[1]

Although forearm fractures may lead to deformity of the wrist and the development of osteoarthritis and the complex regional pain syndrome, there is no evidence of an increase in mortality. Nevertheless, forearm fractures are associated with an increased risk of vertebral and hip fractures in both men and women, so provide an opportunity for consideration of secondary prevention.

Only a third of vertebral fractures come to medical attention, but symptomatic vertebral fractures have a major impact on a patient's quality of life (QOL), because of back pain, loss of height and kyphosis. Vertebral fractures may also result in loss of energy, emotional problems, sleep disturbance, social isolation and reduced mobility. Studies suggest that the impairment of QOL increases with the number of vertebral fractures. The magnitude of the problems encountered by patients with symptomatic vertebral fractures is demonstrated by the fact that they visit their GP 14 times more often than control subjects in the year following fracture. Vertebral fracture is associated with an increased risk of further vertebral fractures, which may be as high as 20% in the following year. There is also an increased risk of hip and other non-vertebral fractures. Vertebral fractures are associated with an excess mortality of 17–20%, which is likely to be due to coexisting conditions associated with osteoporosis, rather than the fracture itself.[1,3]

Hip fractures are the most important fractures in older people, as they cause greater morbidity, higher mortality and more expenditure than all the other fragility fractures combined. Between 25% and 50% of patients become more immobile and dependent after hip fracture, but this is particularly apparent in men and women above the age of 75 years, those with a poor clinical outcome and those who were already dependent before fracture. The excess mortality following hip fractures has been reported to be about 17% over five years, but most deaths occur within six months, suggesting that this is due to complications arising from the fracture and subsequent surgery. Mortality after hip fracture also increases with the number of comorbid conditions. A number of studies show a higher mortality after hip fracture in men than women, but the reason for this is still unclear.[1] It has been estimated that fragility fractures are associated with health and social service costs of £2.3 billion in the UK, almost 90% of which is due tox hip fractures. It has estimated that the average cost of hip

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fracture in the UK is £12 000, of which £4800 is due to the cost of acute hospital care. About 40% of all patients with hip fracture have experienced a prior fragility fracture, potentially representing a lost opportunity for secondary prevention. There is also rapid bone loss after hip fractures and an increased risk of fracture of the contralateral hip and at other sites.

Bone remodelling throughout life

Bone is a living tissue which constantly remodels throughout life, allowing the skeleton to grow during childhood, respond to the mechanical forces placed on it and repair damage due to structural fatigue or fracture. The three major bone cells involved in bone remodelling are osteoclasts, osteoblasts and osteocytes. Osteoclasts are multinucleate cells derived from macrophage-monocyte precursors which resorb bone. Osteoblasts are derived from fibroblast precursors and produce bone matrix or osteoid, which is then subsequently mineralized. Osteocytes are mature osteoblast trapped within calcified bone, which have long interconnecting dendritic processes, and which may serve as mechano-sensory receptors.[1]

Recent research has highlighted the major role of the receptor activator of nuclear factor kappa B (RANK) and RANK ligand (RANKL) system in the regulation of bone remodelling. RANKL is produced by osteoblasts and attaches to RANK on the surface of osteoclasts and osteoclast precursors, leading to osteoclast differentiation and proliferation. The action of RANKL on RANK is blocked by osteoprotegerin (OPG), a decoy receptor produced by osteoblasts and marrow stromal cells. It is now apparent that the beneficial effects of osteoporosis treatments may be mediated in part by changes in the RANK, RANKL and OPG system.[4]

Another regulator of bone turnover is sclerostin, which is produced by osteocyte, under the control of the SOST gene. Sclerostin binds to low density lipoprotein receptor-related protein 5 (LRP5) and inhibits the Wnt signalling pathway, leading to reduced bone formation. Mutations associated with loss of function of the SOST gene lead to sclerosteosis, characterized by increased bone formation, whereas mutations of the LRP5 gene cause the osteoporosis pseudoglioma syndrome.[5]

Pathogenesis of osteoporosis and fractures

BMD at any age is determined by the peak bone mass achieved at maturity, the age at which bone loss starts and the rate at which it progresses. Genetic factors account for up to 80% of the variance in peak bone mass, with the remainder being due to environmental factors, exercise, diet and age at puberty. Bone loss starts between the ages of 35 and 45 in both sexes, but this is accelerated in the decade after the menopause in women. Bone loss then continues until the end of life in men and women, aggravated by factors such as physical inactivity, smoking, alcohol consumption and vitamin D insufficiency, and secondary hyperparathyroidism. There are also a number of causes of secondary osteoporosis, including oral glucocorticoid therapy, male hypogonadism, hyperthyroidism, primary hyperparathyroidism and the use of anti-epileptic drugs.[6]

The risk of fractures is determined by skeletal and non-skeletal risk factors. There is an inverse relationship between bone density and fracture risk, with a two- to threefold increase in fracture incidence for each standard deviation reduction in BMD. The risk of fracture is also determined by other skeletal risk factors, such as bone turnover, cortical and trabecular bone architecture, skeletal geometry and the degree of mineralization of the skeleton. Non-skeletal risk factors for fracture include postural instability, impaired neuromuscular function, physical and mental frailty, and reduced fat and muscle bulk around the hip.[6]

Up to 30% of women and 55% of men with symptomatic vertebral fractures have an underlying cause of secondary osteoporosis, such as oral glucocorticoids, anti-epileptic medication, male hypogonadism, hyperthyroidism, alcohol abuse and myeloma. Risk factors for hip fracture include causes of secondary osteoporosis and conditions associated with falls, such as stroke, Parkinson's disease, dementia and visual impairment.[1,6]

Diagnosis of osteoporosis

Osteoporosis may be diagnosed by performing BMD measurements at the lumbar spine, total hip and femoral neck using dual energy X-ray absorptiometry (DXA). The WHO definition of osteoporosis (T-Score ≤ -2.5) was initially developed for epidemiological studies to assess the prevalence of the condition in different populations, but has increasingly been used as a threshold for diagnosis and therapeutic intervention. Although DXA measurements are generally accurate and precise, lumbar spine BMD may be spuriously elevated in the presence of vertebral fractures, degenerative changes and aortic calcification. Furthermore, only 50% of people with fragility fractures have osteoporosis on DXA scanning, suggesting that other skeletal and non-skeletal risk factors are important in determining fracture risk.

Fracture risk assessment

The WHO has developed a fracture risk assessment tool (FRAX®), which estimates the 10-year risk of fractures of the major fragility fractures (forearm, humerus, spine

and hip) and of hip fracture in particular.[7] Country-specific algorithms use age, gender, weight, height and the presence or absence of appropriately weighted risk factors, with or without femoral neck BMD measurements, to estimate fracture risk. The clinical risk factors for fracture used in FRAX®, which are at least in part independent of BMD, comprise low body mass index (BMI), prior fracture after age of 50 years, parental history of hip fracture, current smoking, oral steroid therapy, alcohol intake >2 units/day and chronic conditions associated with bone loss such as rheumatoid arthritis.[7] Other fracture risk assessment tools are being developed, with a view to identifying people at the highest risk of treatment, in whom to target therapeutic intervention.

Guidance has been developed in the USA, UK and in other countries on the level of fracture risk at which treatment should be considered. This will depend not only on the health economy of the country and the cost of the available therapeutic options, but also individual patient factors such as age and the presence of other comorbid conditions. Most clinical trials of treatments to prevent fractures have recruited participants on the basis of documented osteoporosis or the presence of vertebral fractures. Some clinicians are therefore reluctant to use these treatments at patients at high risk of fracture who have a BMD T-Score > -2.5, as there is no definite evidence that they will prevent fractures in this situation.

Investigation

In patients with documented osteoporosis, underlying causes of bone loss should be identified by careful history, physical examination and appropriate investigation (Table 90.1), particularly when the BMD is lower than expected for age (Z-Score <2.0). These investigations should also be considered in patients with fragility fractures, as specific treatment of underlying conditions such as hyperthyroidism, hypogonadism and primary hyperparathyroidism may increase BMD by up to 15%.[1,6] Investigations for hypogonadism in men may be less appropriate in older men, where the adverse effects of testosterone replacement on the prostate may outweigh the potential benefits. Serum 25-hydroxyvitamin D (25OHD) and parathyroid hormone (PTH) measurements may show vitamin D insufficiency and secondary hyperparathyroidism, but these measurements are probably unnecessary if calcium and vitamin D supplementation is planned. Nevertheless, serum 25OHD and PTH measurements should be considered in patients with possible vitamin D deficiency osteomalacia, which is particularly likely in housebound patients or those with previous gastric resection, malabsorption or the long-term use of anti-epileptic drugs. In patients with severe unexplained osteoporosis, low BMI or anaemia, investigations to exclude a diagnosis of coeliac disease should be performed, particularly if there are symptoms of possible malabsorption.

Table 90.1 Investigations in patients with fragility fractures or low BMD.

Investigation	Finding	Possible cause
Full blood count	Anaemia	Malignancy or malabsorption
	Macrocytosis	Alcohol abuse or malabsorption
ESR and CRP	Raised inflammatory markers	Malignancy
Biochemical profile	Hypercalcaemia	Hyperparathyroidism or malignancy
	Abnormal liver function tests	
	Persistently high AP	Alcohol abuse or liver disease Skeletal metastases
Thyroid function tests	Suppressed TSH; high T_4 or T_3	Hyperthyroidism
Testosterone, SHBG, LH, FSH (men)	Low total testosterone or calculated free testosterone with abnormal gonadotrophins	Hypogonadism
PSA (men with vertebral fractures)	Raised PSA	Metastatic prostate cancer
Serum and urine electrophoresis (Patients with vertebral fractures)	Paraprotein band	Myeloma
Serum 25OHD and PTH	Low 25OHD and raised PTH	Vitamin D insufficiency and secondary hyperparathyroidism.
IgA tissue transglutaminase antibodies (severe osteoporosis, low BMI, anaemia)	Raised antibody levels	Coeliac disease

ESR, erythrocyte sedimentation rate; CRP, C–reactive protein; AP, alkaline phosphatase; TSH, thyroid stimulating hormone; T_4, thyroxine; T_3, triiodothyronine; SHBG, sex hormone binding globulin; LH, luteinizing hormone; FSH, follicle stimulating hormone; PSA, prostate specific antigen; 25OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone; BMI, body mass index.

Lifestyle measures

All patients with documented osteoporosis and/or fragility fractures should be given advice on lifestyle measures to decrease further bone loss, including regular physical activity, eating a balanced diet rich in calcium, smoking cessation, avoiding excess alcohol consumption and maintaining regular exposure to sunlight during the summer months. They should also be advised on measures to reduce the risk of falls. Multidisciplinary falls assessment should also be considered in patients with recurrent falls or abnormal gait and balance.

Drug treatment

The aim of drug treatment is to increase bone density, improve bone strength and reduce the risk of fragility fractures. As bone is a living tissue, treatments target the cells involved in bone remodelling. Most of the currently available treatments are anti-resorptive agents, which act on the osteoclast to decrease bone resorption. Although these treatments lead to a rapid suppression of bone resorption, there is a subsequent reduction in bone formation, because of the close coupling of bone turnover. This leads to a small improvement in BMD, which is then maintained with continuing treatment. In contrast, anabolic treatments act predominantly on the osteoblast to increase bone formation. There may also be a subsequent increase in bone resorption, but the relative imbalance between formation and resorption leads to a greater increase in BMD than that seen with anti-resorptive agents.

A number of treatments for osteoporosis have now been shown in large randomized controlled trials (RCTs) to improve BMD and reduce the risk of fractures (Table 90.2). The choice of treatment will depend on the individual's biological rather than chronological age, BMD, fracture risk, cost and other potential risks and benefits. As compliance and long-term persistence with medication for chronic disease is relatively poor, tolerability and patient preference is also important, as inadequate compliance with osteoporosis treatment is associated with less benefit in terms of BMD and fracture.

Hormone replacement therapy

Hormone replacement therapy (HRT) was previously used widely in the prevention and treatment of younger postmenopausal women with osteoporosis, but this changed with the publication of the results of the Women's Health Initiative Study.[8] Although this showed a reduction in colon cancer, vertebral, hip and other factures, overall the benefits were outweighed by the increased risk of breast cancer, coronary heart disease, stroke and venous thromboembolism. Nevertheless, subsequent subgroup analysis suggests that the adverse effects of HRT may be less in women below the age of 60 years, especially those with a previous hysterectomy who can be treated with unopposed estrogen.

Table 90.2 The effect of osteoporosis treatments on the risk of vertebral, non-vertebral and hip fractures. A indicates that a significant reduction in fractures has been demonstrated in a randomized controlled trial, whereas (A) indicates that a beneficial effect on fractures risk was only found in *post hoc* subgroup analysis. ND indicates that fracture reduction has not been demonstrated.

	Vertebral fractures	Non-vertebral fractures	Hip fractures
HRT	A	A	A
Raloxifene	A	ND	ND
Alendronate	A	A	A
Risedronate	A	A	A
Zoledronate	A	A	A
Ibandronate	A	(A)	ND
Denosumab	A	A	A
Strontium ranelate	A	A	(A)
Teriparatide	A	A	ND
PTH 1–84	A	A	A
Calcium and vitamin D	ND	A	A

Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) have estrogen-like actions on the bone, where they decrease bone resorption and bone loss, but have antagonist actions on the breast and endometrium, thereby decreasing the risk of breast cancer without stimulating endometrial proliferation. Raloxifene decreases the incidence of vertebral fractures, but has no effect on non-vertebral fractures.[9] It is therefore useful in younger postmenopausal women at high risk of vertebral fractures, but less appropriate in older women at significant risk of non-vertebral fractures. Newer SERMs such as lasofoxifene may decrease the incidence of vertebral and non-vertebral fractures, as well as reduce the risk of breast cancer, stroke and cardiovascular disease.[10] Like HRT and raloxifene, lasofoxifene is associated with an increased risk of venous thromboembolism. At the present time, lasofoxifene has not been licensed for the treatment of osteoporosis.

Bisphosphonates

Oral bisphosphonates are currently the treatment of choice for osteoporosis, as they improve BMD and decrease the risk of vertebral, non-vertebral and hip fractures by 35–50%.[11–13] Although these agents are available as daily

(alendronate and risedronate), weekly (alendronate and risedronate) and monthly (ibandronate) preparations, they should be ingested in a fasting condition, to ensure adequate absorption from the bowel. They also need to be taken with water and subsequent recumbency avoided for between 30 and 60 minutes depending on the preparation, to decrease the potential risk of oesophageal side effects of treatment. Oral bisphosphonates are generally well tolerated, but the most common side effects include, acid reflux symptoms, heartburn and indigestions. These may be more likely with alendronate than risedronate, and the clinical studies of the latter included patients with upper gastrointestinal disorders.

The complex instructions for administration, upper gastrointestinal side effects and poor compliance and persistence may limit the use of oral bisphosphonates in some patients. Annual intravenous infusion of zoledronate or three-monthly intravenous injections of ibandronate provide a useful alternative option in this situation. Intravenous zoledronate has been shown to decrease the risk of vertebral fractures by 70% and hip fractures by 41% in women with osteoporosis.[14] A further study in patients with recent hip fracture demonstrated that intravenous zoledronate decreased the risk of vertebral and non-vertebral fractures, but also reduced mortality by 28%.[15] The improvement in mortality was not attributable to the prevention of hip fractures, but may reflect a reduction in deaths due to other conditions. Intravenous bisphosphonate treatment may lead to an acute phase reaction in about 15% of cases, associated with transient 'flu-like symptoms lasting for a few days. The severity of these symptoms can be reduced by the use of paracetamol 1 g four times daily for three days, starting on the day of treatment. As zoledronate has been reported to cause a decline in renal function in patients with pre-existing renal impairment, it should be avoided in the presence of dehydration or when the glomerular filtation rate is less than $35\,ml\,min^{-1}$. As zoledronate is a potent inhibitor of bone resorption it may lead to symptomatic hypocalcaemia in patients with low serum calcium or vitamin D concentrations. If there is any doubt about a patient's vitamin D status, they should receive supplementation before zoledronate is administered.

There has been some concern about potential over-suppression of bone turnover with long-term bisphosphonate treatment. This may lead to structural fatigue and an inability to repair microdamage within the skeleton. Case-series of atypical subtrochanteric fractures of the femur have been reported in patients on long-term bisphosphonate treatment. These atypical fractures are rare and the potential risks appear to be outweighed by the benefits in hip fracture prevention. Nevertheless, the development of prodromal thigh pain in patients on bisphosphonate treatment should alert the clinician to the possible development of an atypical subtrochanteric fracture.

Prolonged bisphosphonate treatment has also been implicated in the development of osteonecrosis of the jaw (ONJ). In this condition, which can occur in the absence of bisphosphonate treatment, there is necrosis of bone in the maxilla or mandible, as a result of occlusion of the blood supply. This results in retraction of the overlying gum and exposure of the necrotic bone. Most cases occur after tooth extraction or other dental surgery, with the remainder occurring mainly in denture wearers, where local trauma and infection may have been implicated. There has been speculation that over-suppression of bone turnover with bisphosphonates may compromise the skeletal response to local trauma and infection, resulting in focal osteonecrosis. ONJ appears to be more common when frequent, high-dose intravenous bisphosphonates are used in the treatment of malignancy (1in 20 to 1 in 100), than with intravenous (1 in 1000 to 1 in 10 000) or oral bisphosphonates in osteoporosis (1 in 10 000 to 1 in 100 000).

Bisphosphonates persist in the skeleton beyond the period of administration, which may result in the maintenance of their beneficial effect on bone density and fracture incidence. As a result of this and concern about the potential adverse effects of long-term treatment, there is increasing debate about the optimal duration of treatment and the possible option of a 'drug holiday'. In the extension phase of the initial clinical trials of alendronate treatment, participants who had taken the bisphosphonate for five years, were randomized to continue treatment or receive placebo for a further five years. Although there was some bone loss and increase in bone resorption five years after stopping alendronate, the BMD was higher and bone turnover markers were lower than baseline values before treatment. Overall, 10 years' treatment with alendronate was not associated with a lower incidence of non-vertebral fractures than five years' treatment followed by placebo, but the risk of clinical vertebral fractures was lower with 10 years' alendronate treatment.[16] A subsequent subgroup analysis demonstrated that in women without a vertebral fracture, continuation of alendronate only decreased the risk of non-vertebral fractures in women whose femoral neck BMD T-Score was still ≤ -2.5 after five years' treatment.[16] Although the number of patients sustaining non-vertebral fractures in this study was relatively small, the results suggest that it may be reasonable to stop alendronate treatment after five years if the patient has a BMD T-Score above -2.5 or is at low risk of vertebral fractures.

Denosumab

Denosumab is a monoclonal antibody directed against RANK ligand. This leads to a marked reduction in bone

resorption and an increase in BMD. A large randomized controlled trial in women with osteoporosis showed that six-monthly subcutaneous injections of denosumab 60 mg decreased vertebral fractures by 68%, non-vertebral fractures by 20% and hip fractures by 40%.[17] The drug appeared to be well tolerated, but there was an increase in eczema and cellulitis in participants treated with denosumab compared with those receiving placebo. There was no increase in cancer, infections or hypocalcaemia in women treated with denosumab over the three years of the study. Although denosumab leads to a substantial reduction in bone resorption, no cases of atypical fractures or ONJ were observed with denosumab, although the latter has now been reported in a patient treated with this drug. In contrast to the situation with bisphosphonates, there is a rapid increase in bone resorption when treatment with denosumab is discontinued. Although this should avoid the potential problem of persistent over-suppression of bone turnover, treatment withdrawal may lead to rapid reversal of any previous improvement in bone density.

Strontium ranelate

Strontium ranelate has been described as a dual-acting bone agent, which reduces bone resorption and increases bone formation. The effects of strontium ranelate on the biochemical markers of bone turnover suggest that the effect on bone resorption is less marked than that seen with bisphosphonates, whereas the effect on new bone formation is more modest than that with anabolic agents. Nevertheless, treatment leads to an improvement in bone strength, even if the underlying mechanism is not readily apparent.

A large clinical trial of three years' treatment with strontium ranelate in women with osteoporosis showed increases in BMD of 12.7% in the lumbar spine and 8.6% in the hip and a 41% reduction in new vertebral fractures.[18] About 50% of the apparent increase in BMD is spurious, due to the incorporation of strontium into the skeleton. Another large study in women with osteoporosis showed a 16% reduction in non-vertebral fractures with strontium ranelate, but a *post-hoc* subgroup analysis in older women with low BMD (T-Score <-3.0) demonstrated a 36% reduction in hip fractures.[19] Strontium ranelate has also been shown to decrease the incidence of vertebral and non-vertebral fractures in women above the age of 80 years, with the benefits extending over a five-year period of treatment.[20]

Strontium ranelate is available in powder form in sachets, the contents of which are dissolved in water. It should preferably be taken at bedtime, at least two hours after eating, to ensure adequate absorption from the bowel. Strontium has been generally well tolerated in clinical trials, but reported side effects have included diarrhoea and a small increased risk of venous thromboembolism, but the reason for the latter remains unclear. In post-marketing surveillance, a small number of cases of drug rash with eosinophilia and systemic symptoms (DRESS) have been reported. This occurred within 3 to 6 weeks of starting treatment, presenting with skin rash, accompanied by a fever and swollen glands.

Parathyroid hormone

Parathyroid hormone (PTH) stimulates bone turnover, with an increase in bone resorption and new bone formation. The continuously high circulating concentration of PTH found in primary and secondary hyperparathyroidism is associated with an increase in bone turnover, but bone resorption is stimulated more than bone formation, resulting in loss of bone from the skeleton. In contrast, intermittent administration of PTH stimulates bone formation more than resorption, resulting in an increase in bone mass and density. There are two licensed PTH preparations available, recombinant human PTH 1–34 (teriparatide) and PTH 1–84, both of which are administered by daily subcutaneous injection.

Clinical studies of PTH treatment show a larger increase in BMD than that observed with bisphosphonates. There is also a stimulation of periosteal new bone formation, leading to a small increase in the diameter of long bones, which may contribute to bone strength. Teriparatide decreases the incidence of vertebral and non-vertebral fractures, but no reduction in hip fractures has been demonstrated.[21] PTH 1–84 has also been shown to reduce the incidence of vertebral fractures.[22] Treatment with PTH is generally well tolerated, but may be associated with transient mild hypercalcaemia, nausea, dizzyness and headaches.[21,22] As these preparations are more expensive than bisphosphonates, their use is generally restricted to patients with severe osteoporosis, or those who fail to respond to bisphosphonate treatment. The anabolic effect of PTH treatment may be attenuated by concomitant administration of a bisphosphonate, but this has not been a consistent finding in clinical studies.

Vitamin D

Vitamin D is essential for musculoskeletal health, as it promotes calcium absorption from the bowel, enables the mineralization of newly formed osteoid tissue in bone and plays an important role in muscle function. There is no universal agreement on what constitutes optimal vitamin D status for musculoskeletal health. Nevertheless, vitamin D insufficiency is common in older people, especially in those who are housebound or living in residential and nursing homes. Vitamin D insufficiency leads to bone loss because of the associated secondary hyperparathyroidism and may

also contribute to an increased risk of falls as a result of muscle weakness and impaired neuromuscular function.[23]

The results of studies of vitamin D supplementation on the risk falls have been inconsistent, but a recent meta-analysis which only included trials where falls were a major outcome measure, demonstrated a 19% reduction in falls with vitamin D in doses of 700–1000 IU daily.[24] The most convincing evidence for the benefit of vitamin D supplementation in fracture prevention was provided by a large study in 3270 women living in nursing homes or sheltered housing, where combined calcium and vitamin D supplementation decreased the risk of hip and other non-vertebral fractures by 43% and 32% respectively.[25] Subsequent studies of vitamin D supplementation, with or without additional calcium, on the risk of fracture have produced conflicting results. Recent meta-analyses suggest that combined calcium and vitamin D supplementation leads to a modest reduction in hip and other non-vertebral fractures, whereas vitamin D alone is ineffective.[26,27]

Although combined calcium and vitamin D supplementation leads to a small decrease in fracture risk, compliance and persistence with supplements containing calcium is relatively poor. Calcium and vitamin D supplementation should therefore be directed on those who are likely to have vitamin D insufficiency, such as care home residents and housebound people living in the community.[28] The use of calcium and vitamin D supplementation should also be considered in people on other osteoporosis treatments, in accordance with recommendations from the National Institute of Health and Clinical Excellence (NICE), unless the clinician is confident that they are calcium and vitamin D replete.[29]

Future treatments

Potential new treatments for osteoporosis which are currently being investigated include cathepsin K inhibitors, sclerostin inhibitors, selective androgen receptor modulators (SARMS) and calcium-sensing receptor antagonists. Cathepsin K is an important enzyme secreted by osteoclasts which resorbs bone. The importance of this enzyme is highlighted by the rare condition of pycnodysostosis (Toulouse-Lautrec syndrome), where a genetic mutation leads to cathepsin K deficiency, associated with the development of dense bones and short stature. The weekly administration of oral odanacatib has recently been shown to reduce the biochemical markers of bone resorption and increase spine and hip BMD in postmenopausal women with low bone density.[30]

Sclerostin is also an important target for the development of new treatments for osteoporosis, as it binds to LRP5 and inhibits the Wnt signalling pathway, leading to reduced bone formation. A recent study of a monoclonal antibody directed against sclerostin has shown an increase in bone formation, bone density and bone strength in cynomolgus monkeys.

SARMS offer the exciting prospect of a treatment which is anabolic for bone and muscle, without unwanted androgenic effects on the prostate in men or virilization in women. Nevertheless, developing a therapeutic agent with the appropriate spectrum of agonist and antagonist actions on the androgen receptor at different sites is likely to be challenging.

Calcium-sensing receptor antagonists or calcilytics are oral agents which lead to the endogenous production of PTH. As noted earlier, continuously raised PTH concentrations in hyperparathyroidism lead to bone loss, whereas pulsatile high concentrations achieved with daily subcutaneous administration of PTH increase bone density. Early work on the effect of calcilytics on bone density have been disappointing, possibly because of a failure to achieve the optimal pulsing of circulating PTH concentrations.

Key points

- Fragility fractures are an important cause of excess mortality, substantial morbidity and health and social service expenditure in older people.
- The risk of fracture is determined by skeletal factors influencing bone strength and by non-skeletal risk factors associated with falls.
- Strategies to prevent fractures should include measures to improve bone strength and reduce the risk of falls.
- A number of osteoporosis treatments have been shown to decrease the risk of fractures. The use of bone density measurements and clinical risk factors for fracture should identify people at the highest risk of fracture, in whom treatment should be considered.

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CHAPTER 91

Gait, balance and falls

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Introduction

Falls and imbalance are important causes of disability, morbidity and mortality in an ageing population. More than one third of adults aged 65 years and older fall each year. Among nursing homes residents, as many as three out of four residents fall each year; 10–20% cause serious injuries. Falls are the leading cause of accidental deaths and account for most of non-fatal injuries and hospital admissions for trauma. The direct cost of fall injuries in 2000 ranged from US$0.2–19 billion.[1] Similar to many other conditions in the geriatric population, factors that can contribute to falls are multiple, and very often more than one of these factors plays an important role. For this reason risk factor assessment, prevention and therapeutic interventions will be the primary focus of this chapter.

Balance

Balance or equilibrium is an ability to maintain the centre of gravity (also known as the centre of mass-COM) of a body within the base of support with minimal postural sway. It is a complex process that depends on the integration of vision, vestibular and proprioception, central coordination and neuromuscular responses that control muscle actions. The senses must detect changes of body position with respect to the base, regardless of whether the body moves or the base moves. When standing, any changes in orientation are perceived by proprioceptive and cutaneous sensors in the feet. Vision detects linear and angular motion of the visual field and the vestibular apparatus detects sway-related linear and angular acceleration of the head. When the support surface is irregular or in motion, vestibular input becomes essential. When the surface is fixed and level, proprioception is predominant. An age-related decline in function can be demonstrated in all parts of this system.

Maintenance of this upright position is associated with postural sway mainly in the anterior/posterior (A/P) direction. Both A/P sway velocity and the area are seen to increase in normal older subjects. Increase in A/P sway has been correlated with spontaneous falls, but a better predictor is mediolateral (side to side) sway. Falls depend on the relationship between the COM and the base of support. In older people, postural reactions controlling the COM are slowed and there appears to be particular difficulty in controlling lateral instability. Moreover, unexpected perturbations require an adjustment of the base of support through compensatory stepping, and older fallers often have problems controlling these compensatory stepping movements. Experiments with a movable platform that can produce multidirectional perturbations show that younger controls react with a rapid compensatory abducting their arms uphill, and hinging at the hips and trunk, thus keeping their COM away from the direction of tilt. In older subjects, compensatory trunk movements are reduced (probably due to stiffening) and their arms are stretched in the direction of the fall.[2]

Peripheral sensation (proprioception and touch) is the most important afferent control mechanism of standing balance in healthy older people. Other factors that are highly correlated with increased sway are reduced muscle strength in the legs, poor near visual acuity, and slowed reaction time. Vision can partially compensate for loss of other sensory inputs, and with increasing age as the postural task gets harder so the reliance on vision becomes greater. Thus, patients with proprioceptive or vestibular impairments are easily upset if the visual field is faulty or misleading in any way. There is no doubt that some individuals maintain good postural control, even into extreme old age, indicating that age-related changes alone have only a minor effect and that imbalance is largely the result of pathology.

[1]This update is based on the excellent chapter by Peter W. Overstall and Thorsten Nikolaus in the previous edition of the book.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Disequilibrium syndromes are identified by inspection of arising, standing, turning and response to perturbation. There are four main syndromes: dysmetria, or lack of coordination of movement associated with cerebellar disorders; bradykinesia, or delayed postural responses associated with akinetic-rigid disorders (parkinsonism); sensory deprivation due to vestibular dysfunction, or loss of proprioception due to peripheral neuropathy; and apraxia, a central disorganization of learned motor programmes for standing and walking, mainly due to frontal lobe dysfunction.[3]

Disease-related balance disorders are also common, such as cerebrovascular, cognitive impairment and Parkinson's disease (PD). Of major importance is the slowing of central coordination due to cerebrovascular or Alzheimer's disease (AD). In its early stages, this is often unrecognized, and the diagnosis is not made until the patient is seen in a falls clinic. In cerebral multi-infarct states patients with few or any neurological signs may present with disequilibrium (during standing and with perturbations) and gait abnormalities (decreased hip and knee flexion during swing phase and instability during stance phase).[4] Minor and even major cognitive impairment is often not considered in the differential diagnosis among recurrent fallers. Balance depends on cognitive processes and attention, which may be affected by anxiety and depression as well as brain pathology. The ability to recover balance demands more attention even for healthy older people when compared with young adults. Older people appear less able to shift weight and select appropriate responses quickly when the environment changes suddenly. The ability to perform multiple or dual tasks is challenged with ageing and becomes diminished in cognitive impairment. One study on institutionalized patients with dementia showed a tendency to stop walking while talking. The difficulties increase as the tasks become more complex, and both the young and the old tend to prioritize gait performance over the secondary cognitive task.[5]

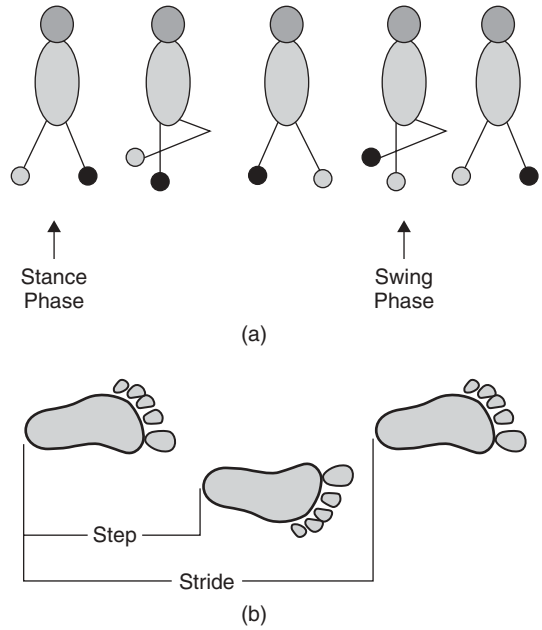

Figure 91.1 The walking gait cycle. (a) During double stance, the weight is transferred from one foot to the other; this is known as the stance phase. During single stance, the centre of mass of the body passes over the foot in preparation for shifting to the other limb, resulting in the swing phase. (b) Step versus Stride. Step is described as the period from initial contact of one limb to the initial contact of the contralateral limb. Stride or gait cycle is described as the period from the initial contact of a particular limb to the point of initial contact of the same limb and is equivalent to one gait cycle. Therefore, there are two steps in each stride.

Gait

Gait is defined as the pattern of movement of the limbs during locomotion over a solid surface, 'manner of walking' or 'sequence of foot movements'. Figure 91.1 illustrates the components of gait cycle.

Human locomotion depends on higher command and control centres in the brainstem and forebrain. Its physiological function depends on the origin of stimuli, either *internal or external cues*. In normal walking–an *internally cued*, well-learned motor act–the supplementary motor area (SMA) of the frontal cortex engages in significant firing just prior to gait ignition. This preparatory activity represents submovement programme selection, which is subsequently sent to the primary motor cortex area (M1). This SMA activity is switched off by phasic activity generated by the basal ganglia (BG), which provides a non-specific cue both to trigger the submovement and to instruct the SMA to prepare for the next. It is this interaction between phasic activity from the BG and SMA, which is responsible for smooth running of predictable, well-learned, automatic movement sequences that depend on internal cues. The sequence of activation, however, is different when movement occurs in response to *external cues*. In this situation the BG/SMA pathways could be bypassed with sensory information from the environment feeding directly into the pre-motor area (PMA) through visual, auditory and propioceptive pathways, with the PMA subsequently activating the M1.[4] The pedunculopontine nucleus (PPN), an area near to the nucleus cuneiformis below the cerebellar peduncle receives afferent connections from the BG, cerebellum and motor cortex and projects to the brainstem reticular nuclei. Then instructions for gait are passed along non-pyramidal pathways in the ventral spinal cord.[6]

Parkinson's disease affects gait by disordered cueing from the BG due to a disturbance in internal rhythm formation in the BG such that the SMA is not switched off

on time. This leads to some of the clinical features of PD including bradykinesia, gait ignition failure and freezing. For this reason PD patients seem to rely heavily on intact sensory/PMA pathways to initiate movements (i.e. better walking while stepping over coloured patterns on the ground and drawing movements when they are aided by external cues). An analogous situation may exist among vascular higher-level gait disorders from infarcts to the aforementioned pathways.[4]

Changes in gait patterns associated with advanced age have been identified, such as slow walking speed due to shorter step length and increased time spent in double limb support. Gait speed declines 12–16% per decade for self-selected gait speed and up to 20% decline for maximum gait speed.[7] These age-related changes in walking patterns have been interpreted as indicating adoption of a more conservative or less destabilizing gait, suggesting that older people compensate for their reduced physical capabilities by being more cautious. Menz and colleagues compared a small sample of young and old subjects and found that old subjects exhibited changes in walking, sensory function and muscle strength. Authors concluded that the normal age-related decline in leg strength may be the primary limiting factor that prevents older people walking at an equivalent speed to younger people.[8]

Gait abnormalities are common in the elderly. An abnormal gait, defined by shuffling or degree of difficulty with turns, was observed in 31% of patients older than 67 years.[6] The factors that affect gait in the elderly may include physiological, medical and social aspects. Individually or in combination, these risk factors predispose elders to gait and balance abnormalities.

Physiological factors include neural control, muscle function and posture control, which are impaired by ageing and/or degenerative disease. Neuromuscular ageing changes are contributors of gait alterations, specifically, the loss of cross-sectional muscle mass (10–40%), decrease in type I and type II muscle fibres, prolonged contraction and relaxation time, and a decrease in conduction velocity in sensory and motor nerves with resultant loss of proprioception. Further, within the articular cartilage, there is formation of cross-links and loss of elastic fibres, resulting in stiffer joint capsules and ligaments that affect the quality of movement and gait. The resultant movement pattern will be slower, more uncertain and uncoordinated, and lacking full range of motion.[7]

Medical factors include the use of psychotropic medications, previous falls, cognitive and neurodegenerative diseases, cardiopulmonary, musculoskeletal, psychological (i.e. depression, anxiety), visual, vestibular and proprioceptive impairments. Along with these factors related to gait impairments the following *social factors* need to be considered as potential contributors to reduced mobility. They consist of self-efficacy or dependence in activities of daily living (ADL), motivation, lack of social support, use of assistive devices and low level of physical activity.[7]

Gait disorders are particularly important in older people because they threaten independence and contribute to falls and injury. A classification of gait disorders based on neural system affected has been proposed.[3,6] The lowest-level gait disorders include peripheral sensory dysfunction with peripheral neuropathy, vestibular, visual and proprioceptive deficits; and peripheral motor dysfunction with arthritis and neuromuscular diseases (focal myopathic, neuropathic weakness). Middle-level gait disorders consist of hemiplegia/paraplegia (arm and leg weakness, spasticity, equinovarus), cerebellar ataxia (poor trunk control, lack of coordination) and extrapyramidal syndromes (rigidity, bradykinesia, trunk flexion). The highest-level gait disorders are: cautious gait, mild AD, cerebrovascular disease and normal pressure hydrocephalus (cognitive impairment, gait apraxia, and urinary incontinence). Nevertheless, a clinical approach seems more useful for physicians to address gait abnormalities. Sudarsky and Nutt present a clinical syndrome classification of seven gait abnormalities: cautious gait, gait limited by weakness, stiff gait, ataxic gait, veering, freezing and toppling gait, and bizarre gaits[3,6] (see Table 91.1).

Falls

A fall, defined by consensus statement as the 'unexpected event in which the patient comes to rest on the ground, floor or lower level',[9] is one of the most common events that threaten the independence of older persons. As with other geriatric syndromes, falls result from the accumulated effect of impairments in multiple domains. The causes of falling often involve a complex interaction among factors intrinsic (medical and neuropsychiatric conditions; impaired vision and hearing; and ageing changes in neuromuscular, gait and balance reflexes) and extrinsic (medications, improper use of assistive device and environmental hazards) to the individual. Rarely is a fall related to a single factor.

Age-related changes in postural control and gait probably play a major role in many falls among older persons. Increasing age is associated with diminished proprioceptive input: slower righting reflexes, diminished strength of muscles, and increase postural sway. All these changes can contribute to falling, especially the ability to avoid a fall after encountering an unexpected trip or hazard. Although ageing changes in gait may not be sufficiently prominent to be labelled truly pathological, they can increase susceptibility to falls. Elderly men tend to develop wide-based, short-stepped gaits; elderly women often walk with a narrow-based, waddling gait.[10]

Although not all elderly individuals with orthostatic hypotension (OH) are symptomatic, this could play a role in causing instability and precipitating falls. People

Table 91.1 Gait syndromes features and disease examples. Clinical syndrome classification of seven gait abnormalities with its features and disease examples.

Gait syndrome	Features	Disease example
Dysmetria	Imbalance with slow and halting gait with wide base of support and irregular progression	Cerebellar ataxia (Friedreich's ataxia), chorea, sensory ataxia
Stiff/rigid	Loss of fluidity, stiffness of legs and trunk with circumduction, scissoring and equinovarus gait.	Spasticity (cerebral palsy, spinal cord disorders), parkinsonism, dystonia, musculoskeletal
Weakness	Waddling, lateral path deviation with regular stride and foot drop	Myopathy, peripheral neuropathy (vincristine, cisplatin chemotherapy, paraproteinemia)
Veering	Deviation of gait or falls on one side	Vestibular disorders, thalamic astasia
Freezing	Start and turn hesitation, stepping movements with side to side shuffling	Multi-infarct, parkinsonism (PD, supranuclear palsy, Lewy body disease, multiple system atrophy)
Cautious	Slowing, short steps, en bloc turns, wider base, shorter swing base	Non-specific, multifactorial
Bizarre/ psychogenic	Embellished, inconsistent, distractible	Anxiety, conversion disorder, fear of falling or space phobia

with orthostatic and/or postprandial hypotension are at particular risk for near syncope and falls, especially when treated with diuretics and antihypertensive drugs. Ooi and colleagues measured supine and standing blood pressure four times in a single day in 844 nursing home residents, both before and after meals. The outcome measure was any subsequent fall over 1.2 years. Fifty percent had OH on at least one measurement. OH did not predict falls in those who had never fallen, but was predictive of recurrence in previous fallers (relative risk 2.6). The timing of OH before or after meals did not affect fall risk. They conclude that OH is an independent risk factor for recurrent falls in institutionalized elderly.[11]

Other pathological conditions, such as degenerative joint disease, can cause pain, unstable joints, muscle weakness and neurological disturbances. Healed fractures of the hip can cause an abnormal and less steady gait. Diminished sensory input, such as in diabetes and other peripheral neuropathies, impaired hearing and visual acuity diminish cues from the environment that normally contribute to stability and thus predispose to falls. Some studies have shown certain gait abnormalities characteristics of patients with dementia and mild cognitive impairment that may lead to falls. Foot deformities (bunions, calluses, nail disease, joint deformities, etc.) can also cause instability and falls.[10]

Across studies, many risk factors were found to be consistently associated with falls. These included age, cognitive impairment, female gender, past history of falls, lower extremity weakness, gait problems, foot disorders, balance problems, hypovitaminosis D, psychotropic drug use and use of four or more prescription medications, arthritis, and PD. The risk of falling consistently increases as the number of these risk factors increases. Among these, previous history of a fall is the strongest risk factor for future falls, with sensitivity of 50%, specificity of 80% and 55% absolute risk of falling during follow-up (RR of 2.4; 95% CI 2.1–2.8) across studies.[12] A history of stroke demonstrated an absolute risk of falling during follow-up of 34% and dementia demonstrated an absolute risk of falling of 47% across studies.

Risk factors might be easily remembered with the mnemonic 'AGAIN I'VE FALLEN' (see Table 91.2).[13] In this way a risk-based assessment can help the clinician approaching geriatric fallers as well as non-fallers.

Table 91.2 Fall risk factors. 'AGAIN I'VE FALLEN' is a mnemonic for risk-based assessment to approach geriatric fallers.

Fall risk factors
Again fallen (previous history of fall)
Gait and balance problems (arthritis, cerebellar disease)
Activities of Daily Living loss
Impaired mental status (cognitive impairment, dementia)
Number and type of drugs (more than four drugs and use of psychotropic, analgesic, diuretic and anti-hypertensive drugs)
Illness (new illness, delirium)
Vestibular disorders
Eyes (glaucoma, retinopathy, cataract), Ears
Foot disorders (bunions, calluses, nail disease, joint deformities)
Alcohol
Lower extremity weakness (stroke, myopathy, deconditioning)
Low blood pressure (orthostatic or postural hypotension)
Environmental hazards (loose rugs, clutter, poor lighting, wet floor, unstable furniture, patient restraints)
Neurological disorders (peripheral neuropathy, stroke, Parkinson's disease, slowed reflexes

Adapted from The Saint Louis University Geriatric Evaluation Mnemonics and Screening Tools (Flaherty and Tumosa[13]).

Clinical presentation of falls

More than half of all falls are related to medical conditions, emphasizing the importance of a careful medical assessment. There are multiple and often interacting causes of falls that include accidents, syncope, drop attacks, dizziness or vertigo, orthostatic hypotension, drug-related and specific disease process.

Accidental

Accidental or unintentional falls occur in less than half of all falls.[1] When people are asked why they fell, by far the most common explanation is that they tripped or slipped. Other causes include a misplaced step, such as stepping into a hole, loss of balance, their legs giving way, or being knocked over. Many attribute their fall to hurrying too much or not looking where they were going; however patients should be screened for poor balance that predisposes to future falls. Addressing the environmental hazards begins with a careful assessment of the environment, like identifying cluttered surroundings and hazards that need to be changed. This may be done by an occupational therapist.

Syncope

Discussion of the complete differential diagnosis of *syncope* is beyond the scope of this chapter. Report of loss of consciousness by the patient or informant helps distinguish syncope or near-syncope as the cause of fall but in most of them the cause for syncope remains unidentified. Common causes of falls associated with loss of consciousness include neurocardiogenic syncope and epilepsy. Neurocardiogenic syncope may be caused by OH, vasovagal syncope, carotid sinus sensitivity, arrhythmias and aortic stenosis. Syncope and seizure are commonly confused, in part because motor activity including clonic jerks frequently follows a syncopal attack. Lempert documented motor activity following syncope in over 90% of healthy volunteers.[14] The most reliable feature that distinguishes 'fit from faint' is the presence of a prolonged post-ictal state. Syncope is transient hypoperfusion, whereas generalized seizures result in slow wave depression of cortical activity, mediated by the thalamus. The slow wave activity persists for minutes to hours following a generalized tonic clonic seizure, whereas cortical activity returns to normal after syncope as soon as perfusion is restored. Tongue biting, incontinence and jerking can be seen in both syncope and epilepsy, so the history both before and after the event is critical to the diagnosis. Many patients with convulsive syncope are erroneously given a diagnosis of epilepsy, and are placed on anticonvulsants for years without a true indication. A reliable witness is invaluable. The patient should be queried about pre-ictal lightheadedness, visual blurring, muffled hearing–all premonitory symptoms of syncope. Patients with unexplained loss of consciousness should undergo tilt table testing to exclude OH, vasovagal syncope, or convulsive syncope (*see* **Chapter 61, Epilepsy**).

Drop attack

A *drop attack* is described as sudden collapse without loss of consciousness. There is no warning. One minute the patient is on his feet, the next he is on the ground without knowing why. Patients often remark on their feeling of helplessness, almost paralysis, when lying on the floor, with immediate recovery once they are helped back onto their feet. However, after any type of fall about a half of older fallers, especially if they are also frail, are unable to get up without help. Causes of drop attacks include medication-induced asterixis (gabapentin, others), OH, cervical cord impingement due to stenosis or other compressive lesions, cataplexy, Ménière's disease, and impaired postural feedback. Although often attributed to vertebrobasilar insufficiency, brainstem ischaemia is rarely proved. Vertebrobasilar ischaemia should only be considered in the presence of the 5 Ds – dizziness, diplopia, dysarthria, dysphagia, dysequilibrium.

Dizziness and vertigo

Dizziness and unsteadiness (described as a sense of imbalance and spinning of head) are common complaints among elders who fall and those who do not fall. In most patients dizziness is multifactorial and 85% of chronically dizzy patients have more than one diagnosis: vestibulopathy, OH, multiple medication effects, primary gait disorders, cerebrovascular and cardiovascular disease, cervical spondylosis, anxiety and poor vision are some of the commonest. Dizziness related to cervical spondylosis results from an imbalance in the flow of stimuli from damaged mechanoreceptors in the cervical spine.

Vertigo (a sensation of rotational movement of surroundings) is probably an uncommon precipitant of falls in the elderly and can be caused by central (brainstem, cerebellum) or peripheral (vestibular) vertigo. Vertigo is also recognized as a feature of migraine. Peripheral vertigo is most commonly associated with disorders of the inner ear, such as paroxysmal positional vertigo (BPPV), acute labyrinthitis and Ménière's disease). Benign paroxysmal positional vertigo should be considered in patients complaining of vertigo provoked by head movements (typically, sitting up or rolling over in bed) because it is one of the few disorders of balance for which there is a simple, safe and effective treatment (*see* **Chapter 87, Disorders of the Vestibular System**). Patients with symptoms suggestive of vertigo will benefit from a thorough otological examination including

auditory testing, which may help clarify the symptoms and differentiate inner ear from CNS involvement.

Orthostatic hypotension

Alterations in blood pressure play a major role in the aetiology of falls. *Orthostatic hypotension* (OH) is identified by taking the blood pressure and heart rate in supine position, within 1 minute in the sitting position and within 3 minutes in the standing position. A drop of more than 20 mmHg in systolic blood pressure or a 10 mmHg drop in diastolic blood pressure is diagnostic of OH.[15] OH may be symptomatic or asymptomatic; however, several conditions can cause OH or worsen it precipitating a fall. For instance, hypovolaemia, heart failure, prolong bed rest, autonomic dysfunction, anaemia and medications. Anaemia is associated with an increase in falls in the nursing home because of orthostasis, but also because it causes decreased mobility, myocardial infarction and frailty. Postprandial hypotension may lead to falls and syncope within two hours following a meal. It appears to be related to an increased release from the gut of vasodilatory peptides. It can be attenuated by giving the antidiabetic drug, acarbose, prior to meals.

Drugs

Drugs that should be suspected of playing a role in falls include diuretics (hypovolaemia), hypoglycaemics, antihypertensives (hypotension), sedatives, antipsychotics (sedation, muscle rigidity, postural hypotension) anticholinergic effects from antidepressants and others.[10] Cardiovascular medications most associated with falls include nitrates, digoxin and type IA antiarrhythmics, calcium-channel blockers, beta-blockers and ACE inhibitors. Among psychotropic medications, consider selective serotonin-reuptake inhibitors (SSRI), tricyclic antidepressants, neuroleptic agents, benzodiazepines and anticonvulsants. A meta-analysis showed that there is a small but consistent association between most classes of psychotropic drugs and falls. The odds ratio for one or more falls with any psychotropic drug use is 1.73.[16] A more recent systematic review of one randomized control and 28 observational studies also showed that psychotropic drugs seem to be associated with an increased risk of falls. Antiepileptics and drugs that lower blood pressure were weakly associated with falls.[17] There is an increased risk of recurrent falls in old people taking more than three or four drugs of any type. In nursing home residents it has been found that three or more medications; having recent change in medication and the presence of antidepressants (SSRI) and anti-anxiety drugs were associated with increased fall risk.[18] For this reason one suggested strategy is to have a consultant pharmacist reviewing medications in all persons with falls in the nursing home.[19]

Disease process

Several *disease processes* are associated with falls, including cardiac arrhythmias, abnormal vision, cerebrovascular, neurodegenerative, cerebellar and spinal cord diseases. Dysrhythmia may manifest with syncope from aortic stenosis or carotid sinus sensitivity. The former indicates valve replacement and the latter indicates increased vagal tone with bradycardia and hypotension, requiring behavioural interventions. Visual loss (acuity 6/18 or worse) detected by standard test of visual acuity is associated with falls and hip fracture. But visual loss by itself requires other postural defects to induce falling, such as impaired limb propioception where patients depend on vision for depth perception.[20] The visual factors that are most strongly predictive of falls are impaired depth perception, contrast sensitivity and low-contrast visual acuity. Stroke does not usually cause loss of consciousness or syncope but falls, yes, and this should be considered only if there are accompanying focal neurological symptoms. Normal pressure hydrocephalus should be considered in patients who present gait instability and falls. The increased stiffness and loss of flexibility of the PD patient increases fall risk. The classic forward-pitched gait (marche de petit pas) reduces stability, and the reduced height of the forefoot from the ground during the swing phase increases the risk of tripping. Mild cognitive impairment (MCI) syndromes have gait abnormalities, such as reduced gait speed and stride length.[21] Patients with dementia have twice the annual incidence of falls compared with cognitively normal older people; their risk of fall-related injuries is high and they have a threefold increase in fractures. Patients are particularly vulnerable during dual tasking and even a simple additional task impairs postural control. This is particularly greater in vascular dementia (79%) and Lewy body dementia (75%) than in AD (25%).[7] Urinary incontinence, urgency and nocturia may cause a distraction, similar to the 'dual-tasking' studies mentioned above, and thereby predispose to falls.[10]

Consequences of falls

Falls in older people are a leading cause of disability, distress, admission to supervised care (like hospital or nursing home placement), and death; it is these consequences that make falls important. Approximately one in ten falls results in a serious injury such as hip fracture, other fractures, subdural haematoma, other serious soft tissue injury, or head injury. Falls are responsible for approximately 10% of visits to the emergency department and 6% of urgent admissions among elderly persons. Nearly 85% of deaths from falls in 2004 were among people older than 75 years. This age group has increase likelihood of admission to a long-term care facility for a year or longer after the fall. Fall fatality rate is higher in men (49%) but fall rate is higher in

women. Twenty to 30% of people who fall suffer moderate to severe injuries such as bruises, hip fractures, or head trauma. These injuries can make it hard to get around and limit independent living, plus they increase the risk of early death. Most traumatic brain injury and fractures among older adults are caused by falls.[1]

Fear of falling (FoF), by itself is considered a risk factor for falls. It refers to the lack of self-confidence that normal activities can be performed without falling. This fear may cause older adults to limit their activities, leading to reduced mobility and physical fitness. The prevalence varies between 21–85% and correlates with female sex and older age.[22] A systematic review by Alarcon *et al.*, suggested using direct questions to the patients to assess for FoF.[23] It has been proposed that FoF may reduce the amount of cognitive resources available for gait and balance control.

Diagnostic assessment

Falls

Inquiry about falls is a vital part of the geriatric assessment. All older people should be asked about falls in the prior year and then those with a single prior fall should have a 'get up and go test'. Those with two or more falls should be given full assessment with history of fall circumstances, medications and medical conditions that might contribute. Then examination of vision, gait and balance, and lower extremity joint function should follow. Basic neurological (mental status, muscle strength, lower extremity sensation, reflexes, test of cortical, extra-pyramidal and cerebellar function) and cardiovascular (heart rate and rhythm, postural pulse and blood pressure, and carotid sinus stimulation test) examination should be included.[24] When evaluating the elderly patient who falls a multifactorial approach has been recommended (Figure 91.2).

Further work-up may be directed to the suspected underlying medical causes of falls. If the history suggests carotid sinus sensitivity, the carotid can be gently massaged for five seconds to observe whether this precipitates a drop (50% reduction) in heart rate or a long pause (two seconds). On the other hand, if gait and balance impairment is suspected the short physical performance battery may be used (see Appendix 91.1). It is a composite of three tests that evaluate balance, gait and lower extremity weakness: standing balance test includes tandem, semi-tandem and side-by-side stands; gait speed test includes two-timed gait speed; and finally the chair stand test with five-time standing and timing. This battery has shown to predict mortality and institutionalization at six years of follow-up in community-dwelling seniors. Along with self-reported activities of daily living (ADL) this tool complements information on elder's functional status and detection of disability.[25]

Brain imaging should be considered if a neurological disorder is suspected, especially high-level gait disorders. Electroencephalography is rarely helpful and is indicated only if there is a high degree of clinical suspicion of seizure. Magnetic resonance imaging (MRI) is frequently obtained to screen for cerebral infarcts, demyelinating disease, posterior fossa malformation, cerebellar degenerations, and hydrocephalus.

Gait

To assess for gait abnormalities, it is important to watch the patient stand from a chair and observe the gait while walking. Gait observation provides a direct assessment of the patient's disability and motor performance problem. There are three suggested screening assessments of mobility, gait and balance. Uniform gait protocols are lacking and diagnosis of gait abnormalities is highly dependent on examiners' expertise. Measuring gait speed is suggested as a simple way to assess health and function in seniors. Verghese showed that each 10 cm s^{-1} decrease in gait speed was associated with a 7% increased risk for falls.[26] In the United States, these techniques have been introduced as Pay-for-Performance measures by the Center for Medicare Services, giving the clinician an additional incentive to screen all elderly patients and document in the chart the results (www.cms.gov).

1 The timed Get Up and Go Test (GUGT) is a simple exam measuring the time it takes a person to rise from a standard arm chair, walk 3 meters (10 feet), turn around, walk back to the chair and sit down (see Appendix 91.2). Patients who require more than 20 s are at high risk for falls. It has a sensitivity of 77% and a positive predictive value of 93% among community-dwelling seniors across observational studies on GUGT's screening ability. In the inpatient setting the sensitivity was 91% but low specificity, 22%.[12] It is a functional measurement easy to perform and the older adult can use an assistive device.

2 Another assessment tool is the Tinetti's Mobility Scale where evaluation of dynamic balance and gait is performed through the performance of 14 tasks (see Appendix 91.3). It is used to identify fall risk in community-dwelling adults. A score less than 24 (score range 0–28) indicates risk for falls. Across observational studies this tool yielded a mean sensitivity of 82% and mean specificity of 65%.[12] This is a long assessment tool, and may be impractical in a busy clinic.

3 Standing unassisted from sitting position, which measures patient's ability to rise from sitting in a chair without using their arms, was found to have 31% of sensitivity and 90% of specificity.[12] The risk of falling increased if a person is unable to stand or requires more than 2 s to do so.

Balance

Doing two things at once ('dual tasking') becomes more difficult in old age; it has been reported that

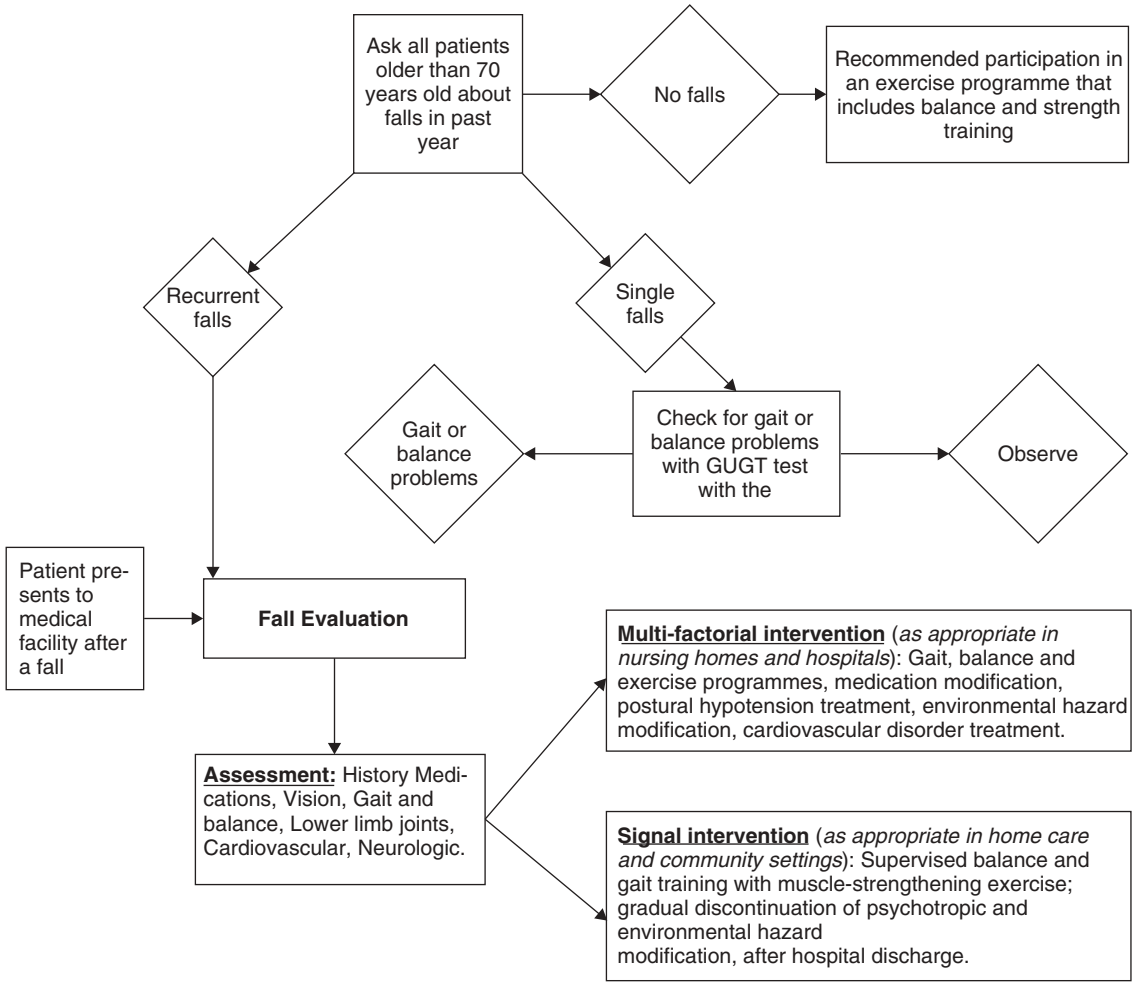

Figure 91.2 The assessment and management of falls. Adapted from AGS/BGS/AAOS Panel on Falls Prevention.[24]

institutionalized older people who were unable to keep up a conversation while walking had a high risk of falls ('stops walking when talking'). Subsequent investigations have shown that dual tasking impairs not only gait but also static and dynamic balance. The difficulties increase as the tasks become more complex, and both the young and the old tend to prioritize gait performance over the secondary cognitive task.[27] For this reason the Saint Louis University Department of Geriatrics has proposed a screening tool for fall risk called dual tasking. It consists of performing one or all of the following tasks: walking speed while counting backward from 100 by sevens; get up and go test while holding a full glass of water; dancing with turn while waltzing; and one leg stand with eyes closed. A gait that worsens when eyes are closed and improves when minor support is given by the examiner is a further clue to proprioceptive problems. Failure to perform either of the dual tasks suggests risk of falling and the patient should be treated with physical therapy. A mini-review by Zijlstra *et al*.[28] demonstrated that dual balance task correlated better with fall prediction than single balance task and had better sensitivity (49%) and specificity (85%) across studies. But no conclusion can be made due to incomplete comparisons among these two measures and variability across studies.

Dynamic standing balance can be measured by the functional reach (FR) test, where the subject stands behind a line and stretches arm as far forward as possible without taking a step. Then the evaluator measures the distance reached and presence of risk of falling is suspected if the patient is able to reach less than 10 inches. This has been shown to correlate with other methods of balance and mobility and also has a relationship with the risk of falls and performance in activities of daily living (ADL). Lin and authors reported that FR significantly predicted a decline in ADL, but it did not predict occurrence of falling (OR 1.00; AUC 0.59).[29]

Therapeutic approach

The American Geriatrics Society and The British Geriatric Society developed in 2001 a set of recommendations for assessing people who fall. Although this initiative may have contributed to a reduction in falls, some of the recommendations have been disproven, like the multifactorial approach and home safety interventions. They might decrease the number of falls but not the rate of falls or injurious falls. Its multifactorial approach makes it costly and less efficient due to less likelihood of compliance. This has led to recent research on single interventions. Furthermore, their application on different settings (community, nursing home and inpatient) has different results in their effectiveness to prevent falls. For this reason, we will discuss the interventions based upon clinical setting in the next section.

Intervention according to underlying disease or causes needs also to be considered. Foot problems can be addressed by podiatric consultation and by changing footwear. Treatment of PD with levodopa and shunting of patients with hydrocephalus remain the most dramatic therapeutic interventions for gait disorders. It is presently unclear to what degree pallidotomy and deep brain stimulation procedures improve gait in PD. Rehabilitation strategies have been explored for gait freezing in patients with PD and in patients with frontal gait disorder. Patients with sensory deficits, who are often at high risk for falls and injuries, often benefit from an intervention such as sensory balance training.[6]

Outpatient setting

Evidence-based guidelines suggested by AGS/BGS/AAOS Panel in 2001 for interventions to reduce risk of falls among community-dwelling populations include review and reduction of medications (specially psychotropics), gait training (with or without assistive devices), and exercise programmes with balance training.[24] Nonetheless, an updated systematic review reinforces and expands current guideline interventions.

A Cochrane Systematic Review on 111 randomized controlled trials, with a total of 55 303 participants revealed that among community-dwelling older people the only intervention that reduced both rate of falling and falling risk was exercise, either as a multiple-component group, Tai chi or individually prescribed home-based multicomponent exercise.[30] These exercise programmes may target strength, balance, flexibility and endurance. Programmes that contain two or more of these components reduced falls risk and rate. Psychotropic medication withdrawal and multifactorial interventions reduced rate of falls but not fall risk. Although drug withdrawal is a complicated intervention that requires the weighing of risks and benefits, its fall reduction effect was well demonstrated by Campbell *et al*.[31] A prescribing modification programme for primary care physicians that entailed ensuring medication review and adjustment reduced risk of falling.[32] Home safety interventions reduced risk of falls in high-risk patients, especially those with severe visual impairment. Common alterations include the installation of locks on cupboards and covers on electrical sockets, improvement of lighting in halls and stairways, and the removal of rugs and other falls hazards. An anti-slip shoe device worn in icy conditions can reduce falls. Similarly, vitamin D supplement reduced falls only in people with lower vitamin D levels. First eye cataract surgery as well as pacemakers in people with carotid sinus hypersensitivity reduced rate of falls.[30]

Results from several randomized controlled clinical trials involving multifaceted fall prevention programmes have yielded encouraging, if not uniform, results. The uneven efficacy could be explained by the variation in combinations of fall reduction interventions. A meta-analysis of multifactorial versus physical exercise-alone interventions revealed that among community-dwelling healthy individuals (without dementia), exercise (i.e. strength, balance training, coordination of movements) decreased fall risk by 55% compared to 10% by multifactorial intervention, and compared to 33% by both interventions (multifactorial and exercise).[33] Interventions were more effective if their duration was less than 12 months, in seniors older than 70 years of age and smaller groups. This may suggest that compliance is better in short-term group programmes as compared to longer-duration individualized programmes. This supports the Cochrane results that the impact of exercise is stronger than multifactorial interventions.

On the other hand, the weak effect on falls found in these two studies may be related to the poor or inefficient implementation of the multifactorial intervention. Therefore, education of physicians is needed. Training clinicians regarding referral to physical therapy or home care for balance and gait problems, performing medication review and reduction, and screening and treating postural hypotension, resulted in a reduction of fall-related injuries by 9% and less fall-related use of medical service by 11%.[32]

Falls have a psychological and social impact that put seniors at risk of disability and death. For this reason multiple studies focus on fear of falling (FoF) and have found effective interventions. A meta-analysis among six randomized control studies indicated that the intervention for more than four months with exercise and education combination was effective in reducing FoF.[34] This result suggests that a combination programme is better than exercise alone because the FoF is influenced not only by physical problems but also by psychological and cognitive issues. They also found that hip protectors did not reduced falls but reduced hip fractures and FoF. Hip protectors appear to improve confidence. The duration of

intervention should be between 4–12 months to provide a programme that will ensure compliance.

Nursing homes

Interventions with demonstrated efficacy in long-term care include comprehensive assessments, staff education, use of and training in assistive devices, and reduction of medications. Preliminary data by Cochrane Systematic Review on interventions for preventing falls in older people in nursing home revealed that multifactorial interventions done by multidisciplinary teams decreased the rate of falls.[35] Further, the effect of multifactorial interventions vary by nursing home subgroups (better in patients with previous history of fall, MCI, urinary incontinence, but not in depressed patients). A review by Vu *et al*. revealed that multifaceted fall prevention programmes were effective in reducing falls by 20–45%. Although fall-risk assessment on admission to long-term care facilities and then quarterly has not been proven to be effective, it continues to be mandated as standard practice in nursing facilities. The authors note that current literature only assesses the effect of environmental assessment/modification, medication assessment/modification, hip protector use and exercise intervention programmes as individual interventions in nursing homes.[36]

Most of the evidence on environmental adjustment focused on restraint reduction as the main intervention. Reduction in restraint use will not decrease fall rate but is associated with reduced likelihood of severe injuries. A simple approach in patients with dementia would be to increase their time in the wander garden (a special care unit with specialized staff and facilities for patients with dementia).

Similarly, authors stressed that a clear association between the use of certain medications and increased fall rates, but no studies examine the effect of medication reduction or elimination on fall rate in nursing home residents.[7] Nevertheless, a systematic review by Sterke *et al*. among 17 observational studies revealed that there is strong evidence of increased fall risk with the use of antidepressants, anxiolytics and use of multiple drugs in nursing home residents with dementia. The evidence on fall risk with withdrawal of psychotropic medications is limited in this subgroup.[37] But there is evidence that among seniors that live in the community the withdrawal of psychotropics has beneficial effects on fall risk.[30] Hip protector use (which are believed to operate under the principle that deflection of forces away from the greater trochanteric process will result in fewer femoral fractures) in nursing homes showed a reduction in hip fractures but not in fall rate.[38]

Exercise programmes (involving strength, balance and flexibility training) for nursing home residents failed to demonstrate a similar effect on falls despite improvement in some objective measures of functional status. The reason for the inability of this intervention to prevent nursing home falls could be related to increased frailty among residents compared with community-dwelling counterparts. A frail nursing home resident offered an exercise regimen increases the risk for falling by becoming more mobile. There is vast evidence of the benefit of exercise in nursing home patients with dementia and cognitive impairment; it improves behaviour and gait. Regardless of this finding a systematic review on fall interventions in the nursing home among seven randomized controlled trials demonstrated inconsistent results on supervised exercise intervention. Vitamin D supplementation reduced fall rate but not risk of falls among nine trials.[35]

Hospital setting

Older adults account for a majority of acute hospitalizations. The risk of falling is certainly a concern in this setting because older people are particularly susceptible to falls during acute illness or exacerbation of chronic disease and one month after hospital discharge. Preliminary data by Cochrane Systematic Review on interventions for preventing falls in older people in hospitals among 10 randomized controlled trials revealed that multifactorial intervention decreased rate of falls as well as risk of falling. Supervised exercise interventions showed a significant reduction in risk of falling. A potential method of reducing falls during hospitalization is through the use of care partners. A large amount of patients at risk of falls in this setting are the patients that suffer stroke. Findings are consistent in stroke rehabilitation that these patients have better outcomes with more intense exercise.[39]

Prevention

From the public health perspective, fall prevention lies across the threshold between primary (avoid fall) and secondary (detect fall risk) prevention. Both preventions have been studied but the most efficient has been the secondary type as discussed in the following section. This is based upon the recognition that it may not be possible to prevent falls completely and what endangers patients is the recurrence of falls more than the risk of falls. Nevertheless, any reduction in fall rate would be expected to also reduce the risk of injurious falls. The US Preventive Services Task Force as well as the European Silver Paper on Health Promotion and Preventive Actions recommends that all persons older than 70 years of age who have known risk factors be counselled about specific measures to prevent falls, encourage physical activity and provide a range of exercise opportunities.

An efficient secondary prevention is education of patient and caregiver. The person at risk and the family should

be educated about the multifactorial nature of most falls, specific risk factors and recommended interventions. Multifactorial assessment followed by interventions targeting the identified risk factors has been the most successful preventive approach. It includes the following components: review and reduction of medications; balance and gait training, muscle-strengthening exercise; evaluation of postural blood pressure; home-hazard modifications; and targeted medical and cardiovascular assessments and treatments. If living alone, the patient should be taught what to do if they fall and cannot get up. A personal emergency response system may be helpful.

Other strategies targeted to persons without history of falls or recent hospitalizations have proved ineffective, such as general exercise programmes, cognitive-behavioural approaches and home-hazard modifications.

There is increasing evidence that vitamin D may be helpful in preventing falls and fractures; even decrease mortality in older people. Therefore, it is appropriate to evaluate patients who fall recurrently for vitamin D deficiency and provide supplement with high dose vitamin D3 (800 IU per day).

Fall clinics

As a response to the importance of falls as a geriatric syndrome, fall clinics where created. They were established in several European countries, Australia, United States and Canada. Equipment and staff make an in-depth examination and assessment of fallers so that relevant physiological and pathological problems can be identified and appropriate interventions organized. In such units, the diagnostic accuracy and effect of interventions is considerably higher than in non-specialized clinics.

Exercise

There are several identified positive effects of exercise including decrease cognitive impairment, improve function, decrease dysphoria and behavioural disturbances, reduce falls, fall injuries and FoF, decrease frailty, reverse sarcopenia, slow bone loss, reduce pain, decrease constipation and incontinence, enhance sleep, improve glycaemic control and QOL. This favours the prescription of exercise by primary care physician no matter what setting they are or how much their patients fall or not. The criterion for a minimal effective exercise dose would equate to a twice-weekly programme running over 25 weeks (using a combining supervised group with interspersed home exercise programmes). Intensity and frequency depends on the patient's fitness. A high-fitness elder may perform 30–60 mins of moderate activity 5–7 days per week. Low-fitness elders should do moderate activity that will increase heart rate 55–69% (or 220-age in males; 220-[0.6 x age] in females). Activity less than 10 minutes may be permitted with gradual increase.[40] In view of the overwhelming evidence on the effectiveness of moderate-high intensity balance training, clinicians may recommend a simple balance exercise. For instance, join dancing or Tai chi group exercise or have the person stand on one leg holding on to a stable object and then shut their eyes four times on each leg.

Key points

DO'S

- Distinguish between falls, syncope and seizure.
- Distinguish between 'dizziness' and true vertigo.
- Assess for correctable underlying causes of falls by history and targeted physical examination.
- Pay particular attention to:
  - Uncorrected vision impairment
  - Orthostatic blood pressure and pulse supine and standing after 3 min
  - Psychotropic medication and quantity of prescribed drugs
  - Gait and balance abnormalities
  - Inappropriate footwear
  - Incorrect use of canes and other assistive devices
  - Environmental hazards
  - A simple 'get up and go' test on all patients who have fallen.
- Ensure safety in recurrent fallers by urgent interventions to prevent injury.
- Refer patients to rehab therapist (physical and occupational) whenever appropriate for detailed environmental and safety assessments, strengthening and proper prescription and use of assistive devices.

DON'TS

- Send all patients for extensive diagnostic studies or cardiac monitoring.
- Test all patients for vitamin D levels.

CONSIDER

- Referring selected patients for Tai chi if they have balance problems and classes available.
- Prescribe vitamin D 800–1200 IU daily.
- Recommending hip protectors in carefully selected nursing home patients who are at high risk for fracture and who are recurrently falling.

Adapted from Kane RL *et al.*[10], Ch. 9, p. 291.

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Appendix 91.1

Short Physical Performance Battery

1. Repeated Chair Stands

Instructions: Do you think it is safe for you to try and stand up from a chair five times without using your arms? Please stand up straight as quickly as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. Please watch while I demonstrate. I'll be timing you with a stopwatch. Are you ready? Begin

Grading: Begin stop watch when subject begins to stand up. Count aloud each time subject arises. Stop the stopwatch when subject has straightened up completely for the fifth time. Also stop if the subject uses arms, or after 1 minute, if subject has not completed rises, and if concerned about the subject's safety.. Record the number of seconds and the presence of imbalance.. Then complete ordinal scoring.

Time: _____sec (if five stands are completed)
Number of Stands Completed: 1 2 3 4 5

Chair Stand Ordinal Score: _____

0 = unable
1 = > 16.7 sec
2 = 16.6-13.7 sec
3 = 13.6-11.2 sec
4 = < 11.1 sec

2. Balance Testing

Begin with a semitandem stand (heel of one foot placed by the big toe of the other foot). Individuals unable to hold this position should try the side-by-side position. Those able to stand in the semitandem position should be tested in the full tandem position. Once you have completed time measures, complete ordinal scoring.

a. Semitandem Stand

Instructions: Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

Grading: Stand next to the participant to help him or her into semitandem position. Allow participant to hold onto your arms to get balance. Begin timing when participant has the feet in

position and lets go.

Circle one number

2. Held for 10 sec
1. Held for less than 10 sec; number of seconds held _____
0. Not attempted

b. Side-by-Side stand

Instructions: I want you to try to stand with your feet together, side by side, for about 10 sec. Please watch while I demonstrate. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop.

Grading: Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and lets go.

Grading

2. Held of 10 sec
1. Held for less than 10 sec; number of seconds held_____
0. Not attempted

c. Tandem Stand

Instructions: Now I want you to try to stand with the heel of one foot in front of and touching the toes of the other foot for 10 sec. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

Grading: Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and lets go.

Grading

2. Held of 10 sec
1. Held for less than 10 sec; number of seconds held_____
0. Not attempted

Balance Ordinal Score: _____

0 = side by side 0-9 sec or unable
1 = side by side 10, <10 sec semitandem

2 = semitandem 10 sec, tandem 0-2 sec

3 = semitandem 10 sec, tandem 3-9 sec

4 = tandem 10 sec

3. 8' Walk (2.44 meters)

Instructions: This is our walking course. If you use a cane or other walking aid when walking outside your home, please use it for this test. I want you to walk at your usual pace to the other end of this course (a distance of 8'). Walk all the way past the other end of the tape before you stop. I will walk with you. Are you ready?

Grading: Press the start button to start the stopwatch as the participant begins walking. Measure the time take to walk 8'. Then complete ordinal scoring.

Time: _____ sec

Gait Ordinal Score: _____

0 = could not do

1 = >5.7 sec (<0.43 m/sec)

2 = 4.1-6.5 sec (0.44-0.60 m/sec)

3 = 3.2-4.0 (0.61-0.77 m/sec)

4 = <3.1 sec (>0.78 m/sec)

Summary Ordinal Score: _____

Range: 0 (worst performance) to 12 (best performance). Shown to have predictive validity showing a gradient of risk for mortality, nursing home admission, and disability.

Source: Guralnik JM *et al*. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol Med Sci* 1994;**49**:M85–M94.

Appendix 91.2

Timed Get Up and Go Test

Measures mobility in people who are able to walk on their own (assistive device permitted)

Name_____

Date_____

Time to Complete_____**seconds**

Instructions:

The person may wear their usual footwear and can use any assistive device they normally use.

1. Have the person sit in the chair with their back to the chair and their arms resting on the arm rests.
2. Ask the person to stand up from a standard chair and walk a distance of 10 ft (3m).
3. Have the person turn around, walk back to the chair and sit down again.

Timing begins when the person starts to rise from the chair and ends when he or she returns to the chair and sits down.

The person should be given 1 practice trial and then 3 actual trial. The times from the three actual trials are averaged.

Predictive Results

Seconds	Rating
<10	Freely mobile
<20	Mostly independent
20-29	Variable mobility
>20	Impaired mobility

Source: Podsiadlo D., Richardson, S. The timed 'Up and Go' Test: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;**39**:142–8.

Appendix 91.3

Tinetti Assessment Tool: Description

Population:	Adult population, elderly patients
Description:	The Tinetti Assessment Tool is a simple, easily administered test that measures a patient's gait and balance. The test is scored on the patient's ability to perform specific tasks.
Mode of Administration:	The Tinetti Assessment Tool is a task performance exam.
Time to Complete:	10 to 15 minutes
Time to Score:	Time to score is included in time to complete
Scoring:	Scoring of the Tinetti Assessment Tool is done on a three point ordinal scale with a range of 0 to 2. A score of 0 represents the most impairment, while a 2 would represent independence of the patient. The individual scores are then combined to form three measures; an overall gait assessment score, an overall balance assessment score, and a gait and balance score.
Interpretation:	The maximum score for the gait component is 12 points. The maximum score for the balance component is 16 points. The maximum total score is 28 points. In general, patients who score below 19 are at a high risk for falls. Patients who score in the range of 19-24 indicate that the patient has a risk for falls.
Reliability:	Interrater reliability was measured in a study of 15 patients by having a physician and a nurse test the patients at the same time. Agreement was found on over 85% of the items and the items that differed never did so by more than 10%. These results indicate that the Tinetti Assessment Tool has good interrater reliability.
Validity:	Not reported
References:	Lewis C. Balance, gait test proves simple yet useful. *P.T. Bulletin* 1993;**2**:9, 40. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *J Am Geriatr Soc* 1986;**34**:119–26.

Tinetti Assessment Tool: Balance

Patient's Name: _____ **Date:** _____

Location: _____ **Rater:** _____

Initial Instructions: Subject is seated in a hard, armless chair. The following maneuvers are tested.

Task	Description of Balance	Possible	Score
1. Sitting Balance	Leans or slides in chair Steady, safe	= 0 = 1	
2. Arises	Unable without help Able, uses arms to help Able without using arms	= 0 = 1 = 2	
3. Attempts to arise	Unable without help Able, requires > 1 attempt Able to rise, 1 attempt	= 0 = 1 = 2	
4. Immediate standing balance (first 5 seconds)	Unsteady (swaggers, moves feet, trunk sway) Steady but uses walker or other support Steady without walker or other support	= 0 = 1 = 2	
5. Standing Balance	Unsteady Steady but wide stance (medial heels > 4 inches apart) and uses cane or other support Narrow stance without support	= 0 = 1 = 2	
6. Nudged (subject at max position with feet as close together as possible, examiner pushes lightly on subject's sternum with palm of hand 3 times.	Begins to fall Staggers, grabs, catches self Steady	= 0 = 1 = 2	
7. Eyes closed (at maximum position #6)	Unsteady Steady	= 0 = 1	
8. Turning 360 degrees	Discontinuous steps Continuous steps Unsteady (grabs, swaggers) Steady	= 0 = 1 = 0 = 1	
9. Sitting Down	Unsafe (misjudged distance, falls into chair) Uses arms or not a smooth motion Safe, smooth motion	= 0 = 1 = 2	
		Balance Score:	

Tinetti Assessment Tool: Gait

Patient's Name: _____ **Date:** _____

Location: _____ **Rater:** _____

Initial Instructions: Subject stands with examiner, walks down hallway or across the room, first at "usual" pace, then back at "rapid, but safe" pace (using usual walking aids).

Task	Description of Gait	Possible	Score
10. Initiation of gait (immediately after told to "go")	Any hesitancy or multiple attempts to start No hesitancy	= 0 = 1	
11. Step length and height	a. Right swing foot does not pass left stance foot with step b. Right foot passes left stance foot c. Right foot does not clear floor completely with step d. Right foot completely clears floor e. Left swing foot does not pass right stance foot with step f. Left foot passes right stance foot g. Left foot does not clear floor completely with step h. Left foot completely clears floor	= 0 = 1 = 0 = 1 = 0 = 1 = 0 = 1	
12. Step Symmetry	Right and left step length not equal (estimate) Right and left step appear equal	= 0 = 1	
13. Step Continuity	Stopping or discontinuity between steps Steps appear continuous	= 0 = 1	
14. Path (estimated in relation to floor tiles, 12-inch diameter; observe excursion of 1 foot over about 10 feet of the course).	Marked deviation Mild/moderate deviation or uses walking aid Straight without walking aid	= 0 = 1 = 2	
15. Trunk	Marked sway or uses walking aid No sway but flexion of knees or back, or spreads arms out while walking No sway, no flexion, no use of arms, and no use of walking aid	= 0 = 1 = 2	
16. Walking Stance	Heels apart Heels almost touching while walking	= 0 = 1	
	Gait Score:		
	Balance + Gait Score:		

Source: Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *J Am Geriatr Soc* 1986;**34**: 119–26.

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CHAPTER 92

Foot problems

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Introduction

Diseases and disorders of the foot and related anatomical structures affect the QOL (quality of life), dignity and the ability of individuals to remain independent and to live life, to the end of life. Foot problems in the older population result from disease, disability and deformity related to multiple chronic diseases as well as focal changes associated with repetitive use and trauma. Older people are at high risk of developing foot-related disease and should receive continuing assessment, education, surveillance and care. The foot is a mirror of health and disease.[1]

The human foot is unique. It evolved to serve as an interface between man and whatever territory he or she most commonly traverses, resulting in a wide range of adaptations to use. Those whose footwear is minimal because of climatic conditions or the nature of territory require little or no covering; have feet that are different from those in industrial civilizations and are related to the needs of society and custom. Feet are required to withstand variable repetitive stress imposed by activities and occupations. The forces of pressure, the adaptations required for ambulation, prior care and the effects of disease and ageing, present different problems in the elderly making comprehensive podogeriatric assessment an essential in patient evaluation and increasing the need for the continuing assessment and examination of the feet and related structures, followed by appropriate care, management, surveillance, education and preventive strategies. All health policies should include appropriate and proper podiatric services.[2]

At one extreme may be the long periods of limited movement that present particular occupational risks. At the other end of the scale may be those occupations, activities and/or interests involving great variability of movement that includes weight/stress-related involvements. All these leave their mark upon the foot in the form of a wide range of morbidities, which usually manifest in later life and produce residual disability in the elderly. Some may produce discomfort or temporary disability. Others will produce insidious but cumulative effects that cause podalgia, ambulatory dysfunction and limitation of activity. As age increases, problems that may have been tolerated in earlier years will limit the mobility of the individual and decrease the QOL. The focus in the management of the older patient may turn from cure to comfort and providing a means to maintain ambulation in order to retain one's independence and dignity.

The feet are covered with hosiery and then thrust into coverings that hide them from view for long periods of time. Footwear, either hosiery or shoes, does not always complement the size and/or shape or function of the foot. Extremes in width, length, last, or depth of the foot will complicate shoe fitting, even with a relatively wide range of mass-produced footwear. This potential functional incompatibility between anatomy and coverings potentiates problems, which become more evident and pronounced in later life. Congenital and/or acquired and disease processes may deform feet in a variety of ways which will result in difficulties throughout life and require proper care over long periods of time to manage these chronic diseases and impairments, such as changes in the circulatory and neurological systems. The primary treatment goals include the relief of pain, restoring the individual to a level of maximum function, and maintaining that function once achieved. Fashion in footwear cannot be disregarded. When style predominates over fit and function, foot problems are again initiated and/or exacerbated due to this functional incompatibility that is many times, with a foot to shoe last (model, design, or shape) incompatibility.[3–5]

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Risk disorders with pedal manifestations

Foot problems and their management are not always regarded as an essential part of some general health programmes or even as being related to general health. The exception is usually related to the catastrophic effects of diabetes mellitus, such as amputation. It is significant but regrettable, that many believe that feet are a part of the body that is designed to hurt. This is true for patients and other elements of the healthcare systems. A majority of patients expect to be able to pursue their normal activities and occupations despite the presence of foot conditions that require rest, but not necessarily hospitalization. With advancing age and the changes in older adult lifestyle, including assisted living and long-term care, these concerns magnify and may be the difference between living life with some quality and sedentary institutionalization. In addition, because of age-related changes and disease, patients are frequently unable to reach their feet because of arthritis, failing eyesight, obesity, postural hypotension, or some other related disorder. Continuing assessment, evaluation and appropriate care is most essential for the 'at-risk' older patients. Tables 92.1 and 92.2 identify some of the primary risks associated with the development of foot problems in the older population (for an example, see also Figure 92.1).

The primary risk diseases that present with significant pedal manifestations as identified by Medicare are summarized in, but not limited to, Table 92.3 as follows:

On 16 June 2009, the Department of Veterans Affairs (VHA Directive 2009-030) expanded the Medicare primary risk categories to appropriately include those conditions listed in Table [92.3A].

A secondary list of systemic 'at-risk' conditions are summarized but not limited to Table 92.4. There are also specialized risks identified in, but not limited to Table 92.5.

Joint diseases such as arthroses, gout, rheumatoid arthritis and osteoarthritis are frequently manifested in the feet. Their primary clinical findings are noted but not limited to those listed in Table 92.6 (gout), Table 92.7 (rheumatoid arthritis), and Table 92.8 (osteoarthritis or degenerative joint diseases).

In the older patient, the consequences of these diseases usually result in deformity, swollen joints, impaired foot function, and an altered and potentially podalgic gait. In many cases, the foot may be the primary site of deformity, disability and limitation of activity that makes weight bearing difficult and causes significant problems in obtaining adequate footwear to compensate for the residuals of these diseases.

Variable and wide-ranging effects accompany endocrinopathies, such as diabetes mellitus, in the cardiovascular and neurological systems. Many of the symptoms and complications associated with the disease are manifested in the feet and produce potential and serious complications in the older patient. The changes involving the foot are the cause for a significant number of potentially life-threatening hospitalizations. In addition, it has been estimated in the

Table 92.1 Generalized risk.

- The process of ageing
- History of diabetes
- Poor glucose control
- History of prior amputation
- Impaired vision
- Inability to bend
- Patients who live alone
- Tobacco use (smoking)
- Dementia and Alzheimer's disease
- History of alcohol use
- Risk-taking behaviour
- Obesity
- Sensory loss, loss of protective sensation and neuropathy
- Altered biomechanics and pathomechanics
- Structural abnormalities including:
  - Limited joint mobility
  - Hallux Valgus
  - Digiti flexi (hammertoes)
  - Prominent metatarsal heads and prolapse (declination)
- Altered gait, ambulatory dysfunction, and fall risk
- Abnormal or excessive foot pressure
- Soft tissue and plantar fat pad atrophy
- Subkeratotic and/or subungual haematoma
- History of previous foot ulcers
- Peripheral arterial and venous disease
- Toenail pathology
- Xerosis and fissures
- Other related chronic diseases and complications
- Cardiovascular disease
- Renal disease
- Retinal disease
- Osteoarthritis
- Rheumatoid arthritis
- Gout

Table 92.2 Other related risks.

- The degree of ambulation
- The duration of prior hospitalization
- Limitation of activity
- Prior institutionalization
- Episodes of social segregation
- Prior care
- Emotional adjustments to disease and life in general
- Multiple medications and drug interactions
- Complications and residuals associated with risk diseases

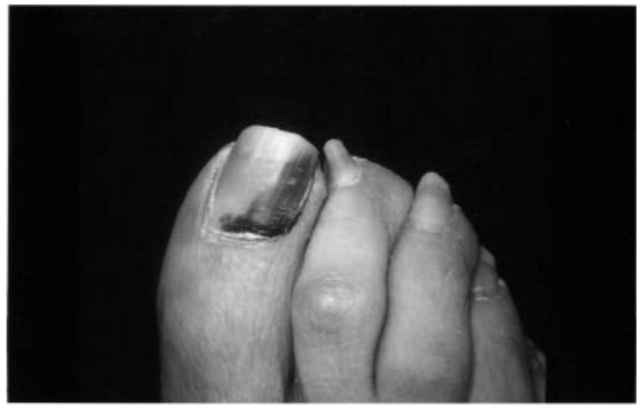

Figure 92.1 Subungual haematoma, onychodysplasia, hammertoes, trophic changes.

Table 92.3 Primary risk diseases.

- Amyotrophic lateral sclerosis (ALS)
- Arteriosclerosis obliterans (ASO, arteriosclerosis of the extremities, occlusive peripheral arteriosclerosis)
- Arteritis of the feet
- Buerger's disease (thromboangiitis obliterans)
- Chronic indurated cellulitis
- *Chronic thrombophlebitis
- Chronic venous insufficiency
- *Diabetes mellitus
- Intractable oedema – secondary to a specific disease (e.g. CHF, kidney disease, hypothyroidism)
- Lymphoedema – secondary to a specific disease (e.g. Milroy's disease, malignancy)
- Peripheral neuropathies involving the feet
- *Associated with malnutrition and vitamin deficiency
- Malnutrition (general, pellagra)
- Alcoholism
- Malabsorption (coeliac disease, tropical sprue)
- Pernicious anaemia
- *Associated with carcinoma
- *Associated with diabetes mellitus
- *Associated with drugs and toxins
- *Associated with multiple sclerosis
- *Associated with uraemia (chronic renal disease)
- Associated with traumatic injury
- Associated with leprosy or neurosyphilis
- Associated with hereditary disorders
- Hereditary sensory radically neuropathy
- Angiokeratoma corporis diffusum (Fabry's)
- Amyloid neuropathy
- Peripheral vascular disease (arterial and venous)
- Raynaud's disease

Note: Those conditions marked with an asterisk (*), require medical evaluation and care within 6 months of their primary foot care service.

Table 92.3A Primary risk categories.

- Documented peripheral arterial disease
- Documented sensory neuropathy
- Prior history of foot ulcer or amputation
- Visually impaired
- Physically impaired
- Neuromuscular disease, i.e. Parkinson's disease
- Severe arthritis and spinal disc disease
- Cognitive dysfunction
- Chronic anticoagulation therapy
- >70 years old without other risk factors
- Diabetes without foot complications
- Obesity

Table 92.4 Secondary risk conditions.

- Collagen vascular disease
- Malignancy
- Lymphoedema
- Postphlebitic syndrome
- Venous (peripheral) insufficiency
- Acromegaly
- Cerebral palsy
- Coagulopathies
- Post-stroke
- Sarcoidosis
- Sickle-cell anaemia
- Reflex sympathetic dystrophy
- Chronic obstructive pulmonary disease
- Hypertension
- Mental illness
- Mental retardation
- Haemophilia
- Patients on anticoagulant therapy
- Paralysis
- Ambulatory dysfunction
- Parkinson's disease
- Immunosuppressed states (HIV, AIDS)

Table 92.5 Specialized risks.

- Vascular grafts
- Joint implants
- Heart valve replacement
- Active chemotherapy
- Renal failure – dialysis
- Anticoagulant therapy
- Haemorrhagic disease
- Chronic steroid therapy

Table 92.6 Gout.

Acute
- Inflammation
- Painful
- Swelling
- Redness
- High uric acid levels
- Podalgia
- Limitation of motion
- Ambulatory dysfunction

Chronic tophaceous gout
- Deformity
- Pain
- Stiffness
- Soft tissue tophi
- Atrophy of soft tissue
- Loss of bone substance
- Gouty arthritis
- Joint deformity
- Excessive pain associated with the acute episodes and
- Exacerbations

Table 92.7 Rheumatoid arthritis.

- Hallux limitus
- Hallux rigidus
- Hallux valgus
- Hallux abducto valgus
- Cystic erosion
- Sesamoid erosion
- Sesamoid displacement
- Metatarsophalangeal subluxation
- Metatarsophalangeal dislocation
- Interphalangeal subluxation
- Interphalangeal dislocation
- Digiti flexi (hammertoes)
- Ankylosis (fused joints)
- Phalangeal reabsorption
- Talonavicular arthritis
- Extensor tenosynovitis
- Rheumatoid nodules
- Bowstring extensor tendons
- Tendon displacement
- Ganglions
- Rigid pronation
- Subcalcaneal bursitis
- Retrocalcaneal bursitis
- Retroachillal bursitis
- Calcaneal ossifying enthesopathy (spur)
- Prolapsed metatarsal heads
- Atrophy of the plantar fat pad
- Soft tissue displacement
- Digiti quinti varus
- Tailor's bunion
- Early morning stiffness
- Pain
- Fibrosis
- Spurs
- Periostitis
- Bursitis
- Plantar fasciitis
- Nodules
- Contracture
- Deformity
- Impairment of function
- Loss or reduction of normal ambulation

United Kingdom and United States, that 50–75% of all amputations relating to the complications associated with diabetes mellitus could be prevented and reduced with an appropriate programme of preventive foot care and foot health education.

The most common clinical findings relating to the diabetic foot are listed but not limited to those in and Table 92.9 (for an example, see also Figure 92.2).

To these problems one must add the effects of repeated microtrauma from footwear, environmental surfaces, lifestyle, neglect and heat-reflecting surfaces, which produce hyperkeratosis and subkeratotic haemorrhage, a predisposing factor for ulceration. Diabetic foot problems in the elderly are characterized by paresthesias, numbness, sensory impairment, a loss of pain sensation, motor weakness, reflex loss, neurotrophic arthropathy, absence of pedal pulses, atrophy, infection, dermopathy, angiopathy, peripheral neuropathy, ulceration and necrosis/gangrene.[6]

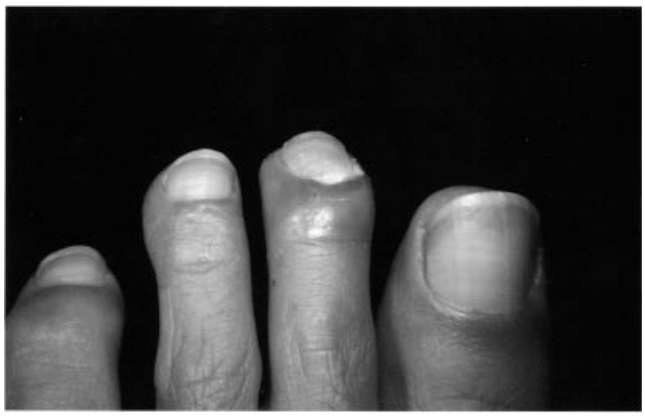

Figure 92.2 Onychia, peripheral arterial disease, early paronychia.

Clinically, the most marked change perhaps for the elderly diabetic is sensory neuropathy. When combined with visual impairment, the elderly can be completely unaware of their feet. Paralysis of intrinsic foot muscles due to motor neuropathy will result in deformities of the toes, claw toes. The bony prominences thus formed on the dorsum of the toes and the plantar aspect of the metatarsophalangeal joints may be the site of skin lesions,

Table 92.8 Degenerative joint diseases: osteoarthritis.

- Pain related to minimal trauma
- Inflammation
- Strain
- Plantar fasciitis
- Spur formation
- Periostitis
- Myofascitis
- Decalcification
- Stress fractures
- Tendonitis
- Tenosynovitis
- Residual deformities
- Pes planus
- Pes cavus
- Hallux valgus
- Digiti flexus (hammertoes)
- Rotational digital deformities
- Joint swelling
- Increase pain
- Limitation of motion
- Reduced ambulatory status

such as hyperkeratosis (tyloma and/or heloma, i.e. corns and calluses), and/or the sites of ulceration, due to pressure, residual subkeratotic haemorrhage and local tissue ischaemia.

The plantar surface of the foot has been the most common site for the development of diabetic ulceration, which is trophic in character. These ulcers develop underneath keratosis with pressure and thus the skilled and proper débridement of the keratosis is a prerequisite to the successful management of the diabetic ulcer and in the prevention of ulcer development (see Figure 92.3). Appropriate weight diffusion and dispersion procedures are also essential elements to management, particularly in the elderly.

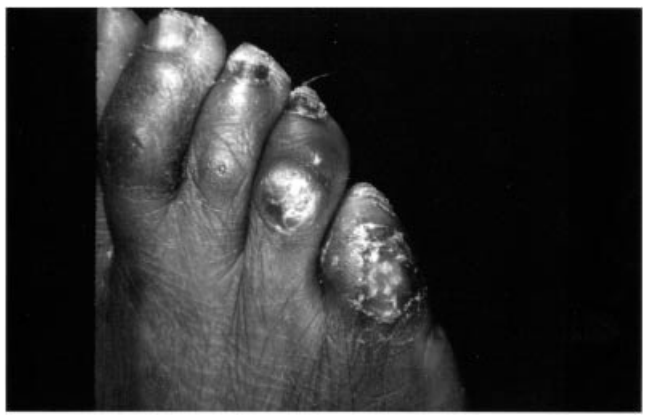

Figure 92.3 Multiple hammer toes, heloma, preulcerative keratosis, subungual haematoma, peripheral arterial disease, trophic changes.

Table 92.9 Diabetic foot changes.

- Vascular impairment
- Degenerative changes related to ageing
- Neuropathy
- Dermopathy
- Atrophy
- Deformity
- Insensitivity
- Podalgia
- Fatigue
- Paresthesia
- Sensory impairment to pain and temperature
- Motor weakness
- Pododynia Dysbasia
- Diminished or lost Achilles and patellar reflexes
- Decreased or vibratory sense (pallesthesia)
- Loss of proprioception
- Neuropathy
- Loss of protective sensation
- Blebs
- Excoriation
- Hair loss
- Xerosis
- Anhidrosis
- Neurotrophic arthropathy
- Neurotrophic ulcers
- Disparity in foot size and shape
- Higher prevalence of infection
- Necrosis
- Gangrene
- Pallor
- Absence or decrease in posterior tibial and dorsalis pedis pulses
- Dependent rubor
- Decreased venous filling time
- Coolness of the skin
- Trophic changes
- Numbness
- Tingling
- Claudication
- Pigmentation
- Cramps
- Pain
- Loss of the plantar metatarsal fat pad
- Hyperkeratotic lesions
- Tendon contractures
- Claw toes (hammertoes)
- Ulceration
- Foot drop
- Diabetic dermopathy (pretibial lesions – shin spots)
- Necrobiosis
- Arthropathy
- Deformity
- Radiographic
    - Thin trabecular patterns
    - Decalcification
    - Joint position change

(*continued overleaf*)

Table 92.9 (*continued*).

- Osteophytic formation
- Osteolysis
- Deformities
- Osteopenia
- Osteoporosis

- Pruritus
- Cutaneous infections
- Dehydration
- Trophic changes
- Fissures
- Onychial changes
- Onychodystrophy
- Diabetic onychopathy (nutritional and vascular changes)
- Onychorrhexis (longitudinal striations)
- Subungual hemorrhage (bleeding in the nail bed)
- Onychophosis (keratosis)
- Onychauxis (thickening with hypertrophy)
- Onychogryphosis (thickening with gross deformity)
- Onychia
- Paronychia
- Onychomycosis (fungal infection)
- Subungual ulceration (ulceration in the nail bed)
- Deformity
- Hypertrophy
- Incurvation or involution (onychodysplasia)
- Splinter haemorrhage (non-traumatic)
- Onycholysis (freeing from the distal segment)
- Onychomadesis (freeing from the proximal segment)
- Autoavulsion

Skin texture and sweating patterns are also markedly altered in the elderly diabetic, due to autonomic neuropathy and oedema. The consequent enlargement of the foot is another cause of epidermal abrasions of the skin from footwear and other forms of trauma and pressure. The management of infection becomes complicated unless appropriate metabolic management is instituted and maintained early in the disease process. The resulting sepsis can lead to necrosis, gangrene and amputation of the limb, which additionally complicates the management of the disease in the elderly as well as necessitating changes in the patient's lifestyle.[7]

Varicose veins are a common manifestation in the legs and feet of the elderly. Varices may be observed on the dorsum of the foot sometimes extending as far as the toes, and also along the medial plantar arch area. Haemosiderin deposited in the skin over the lower one-third of the leg and the foot, giving them a freckled appearance and sometimes imparting a coppery hue where the change becomes marked. Oedema of the foot and ankle also are a frequent accompaniment of varicose veins. Trauma to these vessels can produce haemorrhage. The diminished blood flow resulting from the presence of varicose veins impairs wound healing and causes trophic changes in the skin and nails. Adhesive dressings, even though they may be hypoallergenic, are not well tolerated by such skin for prolonged periods of time. Appropriate treatment may be required to improve both the appearance and function of the extremity.

Complicating factors of venous disease in the elderly include thrombophlebitis, deep venous thrombosis, and postphlebitic syndrome, which produce an 'at-risk' status for the patient with foot problems.

The more common arterial diseases that can be observed in the elderly include the residuals of vasospastic disease, such as Raynaud's disease or phenomenon, acrocyanosis, livedo reticulosis, pernio and erythromelalgia. Occlusive diseases such as arteriosclerosis obliterans, the residuals of thromboangiitis obliterans and related diseases, such as arteritis, periarteritis nodosa, polymyalgia rheumatica, systemic lupus erythematous, erythema nodosum, erythema induratum, nodular vasculitis and hypertensive arteriolar disease. The primary risk factors for the development of peripheral arterial diseases in older patients include smoking, diabetes mellitus, hypertension, Buerger's and Raynaud's diseases. With inadequate perfusion, non-healing wounds, infection, tissue loss and amputation are complications. The primary clinical findings associated with arterial insufficiency are summarized but not limited to those listed in Table 92.10.

In the geriatric patient, arterial insufficiency is heralded by rest pain or nocturnal cramps and/or intermittent claudication. Although it is usually brought on by exercise or use, it may also occur at rest in severe cases of arterial occlusion. Any muscle may claudicate and thus foot pain in the elderly may be related to arterial insufficiency rather than biomechanics or pathomechanics. Painful ulcerations may occur over bony prominences and result from minor trauma and/or pressure. Smoking must be prohibited. Appropriate vascular studies, such as: imaging (arteriography, digital subtraction angiography, MRI, CT arteriography and Doppler imaging), non-invasive studies (Doppler, oscillometric, ankle-brachial index, segmental pressure measurement, plethysmographic waveform analysis, pulse volume recording, skin perfusion pressure, laser Doppler pressure, colour Doppler, ultrasonography, transcutaneous oxygen content (TcPO3), cutaneous oximetry and treadmill exercise testing), and surgical consideration should be provided when pain is uncontrolled and/or when ulceration and infection are significant.

Because of the risk involved in the geriatric patient and the relationship to multiple chronic diseases, assessment, examination and evaluation of the feet and related structures, are essential. Elements of this process include needs, relationships to ambulation and activities of daily living (ADL), instrumental activities of daily living (IADL), and the fact that foot pain can result in functional disability, dysfunction and increased dependency.

Table 92.10 Primary clinical vascular findings.

Fatigue
Rest pain
Coldness
Decreased skin temperature
Burning
Colour changes
Absent or diminished digital hair
Tingling
Numbness
Ulceration
History of phlebitis
Cramps
Oedema
Claudication
History of repeated foot infections
Diminished or absent pedal pulses
Popliteal and/or femoral pulse change
Colour changes – rubor – erythema and/or cyanosis
Temperature changes – cool – gradient
Xerosis, atrophic and dry skin
Atrophy of soft tissue
Superficial infections
Onychial changes
Onychopathy
Onychodystrophy
Nutritional changes
Subungual haemorrhage
Discolouration
Onycholysis
Onychauxis (thickening)
Onychorrhexis (longitudinal striations)
Subungual keratosis
Deformity
Blebs
Varicosities
Delayed venous filling time
Prolonged capillary filling time
Femoral bruits
Ischaemia
Necrosis and gangrene

A Comprehensive Podogeriatric Assessment Protocol (Helfand Index), has been developed by the Pennsylvania Department of Health in cooperation with Temple University, School of Podiatric Medicine and is included as Table 92.11.

In addition, Medicare in the United States has three additional sets of criteria for Class Findings required to qualify for primary foot care (Table 92.12); Criteria for Therapeutic Shoes for Diabetics (Table 92.13); Criteria of the Loss of Protective Sensation (LOPS) (Table 92.14); Criteria for Onychomycosis (see Figure 92.4) (Table 92.15).

A systems review of known chronic and risk diseases is a key element in the assessment process. Conditions such as

Table 92.11 Podogeriatric assessment protocol developed under a contract to the Pennsylvania Department of Health as the 'Helfand Index' by Arthur E. Helfand, DPM. Reproduced with permission.

Date of visit MR#
Patient's name Age
Date of birth Social Security #
Address
City State Zip code
Phone number
Sex M F Race B W A L NA
Weight in Pounds Height in Inches
Social status M S W D SEP
Name of primary physician/health-care facility
Date of last visit
History of Present Illness
Swelling of feet Location
Painful feet Quality
Hyperkeratosis Severity
Onychial Changes Duration
Bunions Context
Painful toe nails Modifying factors
Infections Associated signs and symptoms
Cold feet
Other
Past History
Heart disease Diabetes mellitus
High blood pressure * IDDM
Arthritis * NIDDM
* Circulatory disease Hypercholesterol
Thyroid
Gout
Allergy
History of Smoking – Alcohol – Substance Abuse
Family – Social
Systems Review
Constitutional
ENT
Card/Vasc
GU
Eyes
Musculo-Skeletal
Neurologic
Skin – Hair – Nails
Skeletal Endocrine
Respiratory
GYN
GI
Psychiatric
Allergic
Immunologic
Hematologic
Lymphatic
Medications

(*continued overleaf*)

Table 92.11 (*continued*).

Dermatologic
- * Hyperkeratosis
- Xerosis
- Onychauxis B-2-b
- Tinea pedis
- Infection
- Verruca
- * Ulceration Hematoma
- Onychomycosis
- Rubor
- Onychodystrophy
- * Preulcerative
- * Cyanosis B-2-e
- Discolored

Foot Orthopedic
- * Hallux valgus
- * Hallux rigidus-limitus
- * Anterior imbalance
- * Morton's syndrome
- * Digiti flexus
- Bursitis
- * Pes planus
- * Prominent Metatarsal Head
- * Pes Valgoplanus
- * Charcot joints
- * Pes cavus
- Other

Vascular Evaluation
- * Coldness C-2
- * Claudication C-1
- * Trophic changes B-2-a
- Varicosities
- * DP absent B-3
- * PT absent B-1
- * Amputation
- * Night cramps
- * AKA BKA FF T A-1
- * Edema C-3
- Atrophy B-2-d
- Other

Neurologic Evaluation
- * Achilles
- * Superficial plantar
- * Vibratory
- * Joint Position
- * Sharp/Dull
- * Burning C-5
- * Paresthesia C-4
- Other

Risk Category – Neurologic
- 0 = No Sensory Loss
- * 1 = Sensory Loss
- * 2 = Sensory Loss and Foot Deformity
- * 3 = Sensory Loss, Hx Ulceration, and Deformity

Table 92.11 (*continued*).

Risk category – Vascular
- 0 – 0 No Change
- * I – 1 Mild Claudication
- * I – 2 Moderate Claudication
- * I – 3 Severe Claudication
- * II – 4 Ischemic Rest Pain
- * III – 5 Minor Tissue Loss
- * III – 6 Major Tissue Loss

Class Findings
- A1 Nontraumatic Amputation
- B1 Absent Posterior Tibial
- B2 Advanced Trophic Changes
- B2a Hair Growth (Decrease or Absent)
- B2b Nail changes (Thickening)
- B2c Pigmentary Changes (Discoloration)
- B2d Skin Texture (Thin, Shiny)
- B2e Skin Color (Rubor or Redness)
- B3 Absent Dorsalis Pedis
- C1 Claudication
- C2 Temperature Changes (cold)
- C3 Edema
- C4 Paresthesia
- C5 Burning

Onychomycosis: Documentation of mycosis/dystrophy causing secondary infection and/or pain, which results or would result in marked limitation of ambulation.
- Discoloration
- Hypertrophy
- Subungual Debris
- Onycholysis
- Secondary Infection
- Limitation of Ambulation and Pain

Classification of Mechanical or Pressure Hyperkeratosis – Grade Description
- 0 No lesion
- 1 No specific tyloma plaque, but diffuse or pinch hyperkeratotic tissue present or in narrow bands
- 2 Circumscribed, punctate oval, or circular, well defined thickening of keratinized tissue
- 3 Heloma miliare or heloma durum with no associated tyloma
- 4 Well-defined tyloma plaque with a definite heloma within the lesion
- extravasation, maceration, and early breakdown of structures under the tyloma or callus layer
- 5 Complete breakdown of structure of hyperkeratotic tissue, epidermis, extending to superficial dermal involvement

Plantar keratomata pattern
- LT 5 4 3 2 1
- RT 1 2 3 4 5

Ulcer classification
- Grade – 0 – Absent skin lesions
- Grade – 1 – Dense callus but not preulcer or ulcer
- Grade – 2 – Preulcerative changes
- Grade – 3 – Partial thickness (superficial ulcer)

(*continued overleaf*)

Table 92.11 (*continued*).

Grade – 4 – Full thickness (deep) ulcer but no involvement of tendon, bone, ligament or joint
Grade – 5 – Full thickness (deep) ulcer with involvement of tendon, bone, ligament or joint
Grade – 6 – Localized infection (abscess or osteomyelitis)
Grade – 7 – Proximal spread of infection (ascending cellulitis or lymphadenopathy)
Grade – 8 – Gangrene of forefoot only
Grade – 9 – Gangrene of majority of foot
Onychial Grades at Risk
Grade I Normal
Grade II Mild hypertrophy
Grade III Hypertrophic
Dystrophic
Onychauxis
Mycotic
Infected
Onychodysplasia
Grade IV Hypertrophic
Deformed
Onychogryphosis
Dystrophic
Mycotic
Infected
Footwear Satisfactory Hygiene satisfactory
Yes
No
Hygiene Satisfactory
Yes
No
Stockings
Nylon
Cotton
Wool Other
None
Assessment
Plan
Podiatric referral
Patient education
Medical referral
Special footwear
Vascular studies
Clinical lab
Imaging
Rx

Notes: B, Black; W, White, A, Asian; L, Latino/Hispanic; N/A, Native American; S, Single; M, Married; W, Widow/Widower; D, Divorced; S, Separated; DP, Dorsalis pedis pulse; PT, Posterior tibial pulse; AKA, Above the knee amputation; BKA, Below the knee amputation; FF, Forefoot amputation; T, Toe amputation; Hx, History of; Rx, Prescription for treatment as a part of the key to data analysis and risk stratification, the key notes of number and letter (i.e. 2-a) indicate Medicare class findings as risk factors and those noted with an asterisk (*) identify risk factors to qualify patients for therapeutic shoes under Medicare.

Table 92.12 Medicare Class Findings.

Class Findings
Class A findings
Non-traumatic amputation of foot or integral skeletal portion thereof
Class B findings
Absent posterior tibial pulse
Absent dorsalis pedis pulse
Advanced trophic changes as (three required)
Hair growth (decrease or absence)
Nail changes (thickening)
Pigmentary changes (discolouration)
Skin texture (thin, shiny)
Skin colour (rubor or redness)
Class C findings
Claudication
Temperature changes (e.g. cold feet)
Oedema
Paresthesias (abnormal spontaneous sensations in the feet)
Burning

Table 92.13 Therapeutic shoe criteria.

• History of partial or complete amputation of the foot
• History of previous foot ulceration
• History of pre-ulcerative callus
• Peripheral neuropathy with evidence of callus formation
• Foot deformity
• Poor circulation

Table 92.14 Onychomycosis: Documentation of mycosis/dystrophy causing secondary infection and/or pain, which results or would result in marked limitation of ambulation.

• Discolouration
• Hypertrophy
• Subungual debris
• Onycholysis
• Secondary infection
• Limitation of ambulation and pain
• Dystrophic
• Onychodysplasia
• Onychauxis
• Onychogryphosis

diabetes mellitus, arteriosclerosis, anaemia, chronic renal disease, CHF, arthritis, stroke and neurological deficits are examples of these risk conditions. The patients' living conditions should also be noted as they are a relationship to care and needs. The chief complaint of the patient should be identified related to their daily lives in terms of activity

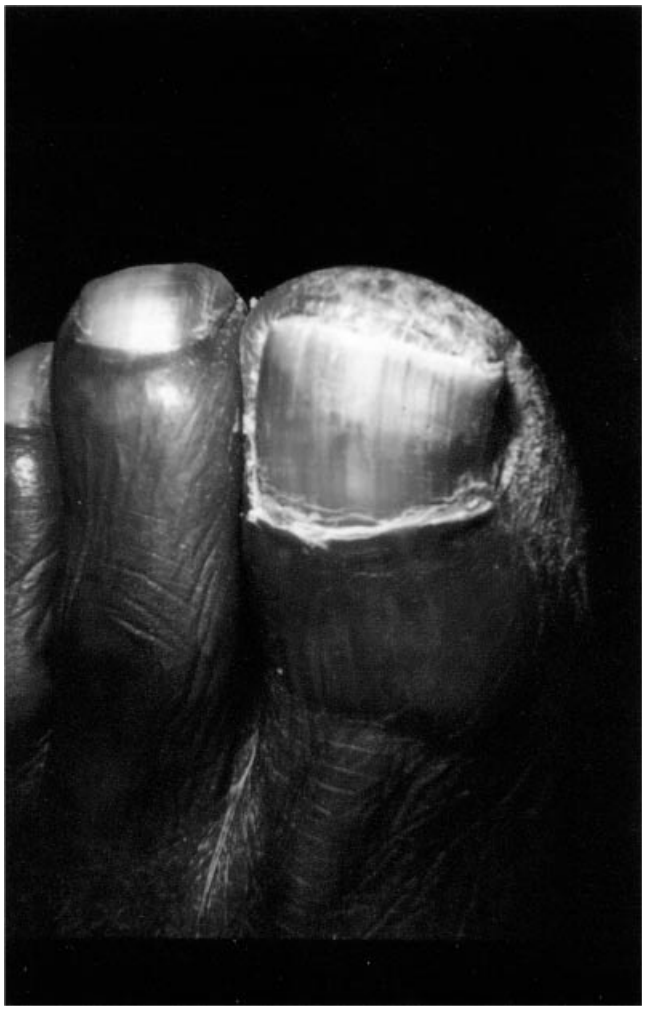

Figure 92.4 Onychomycosis, onychauxis, xerosis, onychorrhexis, and peripheral arterial disease.

and social needs. The duration, location, severity, prior treatment and results should also be identified in relation to the presented condition. A social history is also a part of this assessment process.

The dermatological symptoms and signs and the onychial findings are listed but not limited to Tables 92.16 (see also Figure 92.5) and 92.17.

The neurological symptoms and signs are included but not limited to Table 92.18. The vascular findings are noted in Table 92.10.

A drug history and summary of findings, clinical impressions and special notations for some of the primary basics for assessment, as anticoagulants, steroids and medications to control diabetes mellitus present additional risk.

The primary musculoskeletal clinical findings are noted but not limited to Table 92.19.

There are biomechanical and pathomechanical factors that combine with structural abnormalities and deformities to increase the risk for pedal ulceration. They are listed but not limited to Table 92.20.

The forefoot (metatarsals and phalanges) is the most mobile part of the foot and the majority of problems that develop occur in this area. Pressure from deformities and shoe to foot incompatibility, will give rise to keratotic lesions as an initial response to pressure and friction, but footwear is by no means the only cause of painful lesions in the feet or the prime aetiological factor. Congenital and acquired deformities will result in malfunction and dysfunction and give rise to secondary lesions as the body attempts to compensate for pain and deformity. Alteration in shape and function can arise from trauma, paralysis, changes in function as a result of surgical revision and/or diseases, such as arthritis, which embarrass normal function. The mobility of the foot has a great influence on the type and extent of painful secondary foot lesions.

Table 92.15 Loss of protective sensation (LOPS).

Services furnished for the evaluation and management of a diabetic patient with diabetic sensory neuropathy, resulting in a LOPS must include the following:

1 A diagnosis of LOPS
2 A patient history
3 A physical examination consisting of findings regarding at least the following elements:
   a Visual inspection of the forefoot, hindfoot and toe web spaces
   b Evaluation of protective sensation
   c Evaluation of foot structure and biomechanics
   d Evaluation of vascular status
   e Evaluation of skin integrity
   f Evaluation and recommendation of footwear
4 Patient education

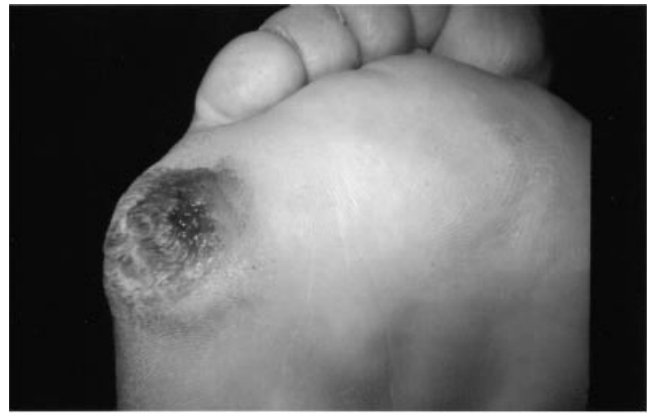

Figure 92.5 Preulcerative keratosis, subkeratotic haematoma, digiti quinti varus, metatarsal prolapse, anterior plantar fat pad displacement.

Table 92.16 Dermatological findings.

Exquisitely painful or painless wounds
Slow healing or non-healing wounds
Trophic ulceration
Necrosis
Skin colour changes such as cyanosis or redness
Changes in texture and turgor
Pigmentation
Haemosiderin deposition
Chronic itching – pruritus
Neurogenic, and/or emotional dermatoses
Contact dermatitis
Stasis dermatitis
Atopic dermatitis
Nummular eczema
Scaling
Xerosis or dryness
Excoriations
Recurrent infections
Paronychia
Tinea pedis
Onychomycosis
Pyoderma
Cellulitis
Keratotic dysfunction
Keratotic lesions without haemorrhage or haematoma
Tyloma (callus)
Heloma durum (hard corn)
Heloma miliare (seed corn)
Heloma molle (soft corn)
Heloma neurofibrosuum (neuritic)
Heloma vasculare (vascular)
Onychophosis (callus in the nail groove)
Intractable plantar keratosis
Keratotic lesions with haemorrhage or haematoma (pre-ulcerative)
Verruca
Psoriasis
Fissures
Hyperhidrosis
Bromidrosis
Maceration
Diminished or absent hair growth
Diabetic dermopathy
Necrobiosis lipoidica diabeticorum
Bullous diabeticorum
Poroma
Absence of hair
Ulceration

Table 92.17 Onychial findings.

Onychoatrophia (atrophy)
Onychia sicca (dryness)
Onycholysis (freeing from the free edge)
Subungual hyperkeratosis
Onychexallis (degeneration)
Diabetic onychopathy
Onychauxis (hypertrophy)
Onychogryphosis (hypertrophy and deformity)
Onychomycosis (fungal infection)
Onychia
Paronychia
Onychitis (inflammation)
Onychalgia (pain)
Subungual abscess
Subungual heloma (keratosis)
Subungual exostosis
Periungual verruca
Onychophyma (painful degeneration with hypertrophy)
Onychomadesis (freeing from the proximal portion)
Onychoschizia (splitting)
Onychyphemia (haemorrhagic)
Onychoclasis (cracking)
Onychomalacia (softening)
Onychoptosis (shedding)
Subungual spur
Onychophosis (hyperkeratosis in the nail groove)
Subungual haematoma
Splinter haemorrhage
Onychocryptosis (ingrown toenail)
Periungual ulcerative granulation tissue
Onychodysplasia (involuted or pincer nails)
Onychodystrophy (trophic changes)
Onychorrhexis (longitudinal ridging)
Beau's lines (transverse growth cessation)
Pterygium (hypertrophy of eponychium)
Onychoclasis (breaking of the nail)
Diabetic onychopathy (trophic diabetic changes)
Hypertrophic onychodystrophy

Rigid feet usually have circumscribed areas of hyperkeratosis. Mobile feet have more extensive areas of keratotic development. Where the foot is deficient in fibro-fatty padding or where the stress is chronic, constant and severe, the so-called neurovascular heloma or tyloma may develop, creating a disruption in the normal dermal–epidermal relationship. Small blood vessels and nerve endings then extend into the epidermis and are enveloped in the keratotic lesion, creating excessive pain and complicating management. Such lesions may be completely disabling and in some patients, result in distressing hyperaesthesia that is difficult to manage.

Footwear can also reveal a great deal about disease and dynamic foot function. Neglected footwear generally demonstrates neglected foot care and may indicate social poverty. It may also demonstrate poor eyesight. Urine splashes that have dried on the uppers of shoes are sometimes the first indication of occult diabetes mellitus.

Table 92.18 Neurological findings.

Sensory changes
Burning
Tingling
Clawing sensations
Pain and hyperactivity
Two-point discrimination
Motor changes
Weakness
Foot drop
Autonomic
Diminished sweating
Hyperhidrosis
Sensory deficits
Vibratory
Proprioceptive
Loss of protective sensation
Changes in pain and temperature perception
Hyperaesthesia
Diminished to absent deep tendon reflexes (Achilles and Patellar)
Hypohidrosis with perfusion
Diabetic dermopathy or pretibial lesions (shin spots)
Thickened skin with calluses under high-pressure areas, demonstrating an intrinsic minus foot (marked digital contractures, metatarsal prolapse, prominent metatarsal heads, and plantar fat pad atrophy and displacement)
Bowstring tendons
Charcot foot

Table 92.19 Musculoskeletal findings.

Gradual change in shape or size of the foot
A sudden and painless change in foot shape with swelling and no history of trauma
Cavus feet with claw toe
Drop foot
'Rocker bottom foot' or Charcot foot
Neuropathic arthropathy
Elevated plantar pressure
Decreased muscle strength
Decreased ranges of motion
Multiple foot deformities
Limited joint mobility
Abnormal foot pressure and subsequent ulceration
Structural abnormalities or foot deformities
Hammertoes
Claw toes
Prominent metatarsal heads
Atrophy of plantar fat pad
Plantar fat pad displacement
Foot muscle atrophy
Hallux valgus
Hallux limitus
Hallux rigidus
Tailor's bunion
Plantar Fasciitis
Spur formation
Calcaneal spurs
Bursitis
Periostitis
Decalcification
Stress fractures
Tendonitis
Tenosynovitis
Metatarsalgia
Morton's syndrome
Joint swelling
Bursitis
Haglund's deformity
Neuritis
Entrapment syndrome
Neuroma
Sesamoid erosion
Sesamoid displacement
Tendo-Achilles contracture
Digital amputation
Partial foot amputation
Charcot's joints
Phalangeal reabsorption
Functional abnormalities
Pes cavus
Equinus
Pes planus
Residuals of arthritis (degenerative, rheumatoid and gouty)
Biomechanical and pathomechanical variations
Gait evaluation

(*continued overleaf*)

Keratotic lesions

The presence of hyperkeratotic lesions, such as tyloma and/or heloma (callous or corns) on the foot is associated with some degree of malfunction of the foot, especially in the elderly. Elimination and/or management of the underlying causes are the principle objective of therapy. There are a wider range of treatment options to be considered including continuing surveillance, monitoring and primary management including débridement, pressure reduction, orthotics, shoe modification and surgical revision of deformities, usually when conservative measures are unresponsive. It is the same approach as utilized for any other chronic condition.[8]

The normal response of the epidermis to intermittent, chronic pressure and/or stress is to increase in thickness. The resulting hyperkeratosis may be both hyperplastic and hypertrophic. These lesions commonly occur on the plantar aspect of the metatarsophalangeal joints, the hallux, the margins of the heel, the dorsum of the toes, especially with contracture, and in the nail grooves. Atrophy of the adjacent dermis and soft tissue is common especially in the

Table 92.19 (*continued*).

Shoe evaluation
Type of shoe
Fit and size
Shoe wear and patters of wear
Shoe lining wear
Foreign bodies
Insoles
Orthoses

Table 92.20 Factors leading to ulceration.

- Body mass
- Gait
- Ambulatory speed
- Tissue trauma
- Weight diffusion
- Weight dispersion
- Pathomechanics, defined as structural change in relation to function
- Biomechanics, defined as forces that change and affect the foot in relation to function
- Imbalance, defined as the inability to adapt to alterations of stress
- Force – alteration in physical condition, either shape or position
- Compression stress – one force moves toward another
- Tensile stress – a pulling away of one part against another
- Shearing stress – a sliding of one part on the other
- Friction – the force needed to overcome resistance and usually associated with a sheering stress
- Elasticity – weight diffusion and weight dispersion
- Fluid pressure – soft tissue adaptation and conformity to stress

patient demonstrating a LOPS. With continuing pressure and neurovascular involvement, fibrous tissue may develop to bind the skin to the underlying joint capsule and/or tissues.

Patients with diabetic peripheral neuropathy involving the lower extremities also present with reported numbness or a reduced ability to feel pain and/or temperature changes; tingling, burning, or prickling sensations; sharp, jabbing, or electric shock like pain that is magnified at night; extreme sensitivity to light touch; loss of balance and/or coordination; muscle weakness, pain and ambulatory dysfunction (pododynia dysbasia); and serious complications, such as ulceration, infection, Charcot's deformity, and significant risk of amputation.[9]

Subkeratotic haematomas indicate areas where blood has been forced from vessels and are indicative of extensive pressure and/or a complication of an associated systemic disease, such as diabetes mellitus. Occasionally, this makes a 'lake' in the area and produces a moist, shallow ulceration, which usually dries and heals when the area is débrided of keratosis and appropriately managed.

The characteristic of a heloma durum (hard corn) is the presence of a nucleus. Heloma represent a reaction to more localized stress than is the case with tyloma (callosity). Heloma may also present as a central area in a tyloma. The nucleus is small and may be circular or even crescentic in shape. It is harder due to increased density than the surrounding hyperkeratosis. The nucleus may represent parakeratotic changes histologically, similar to that which occurs in psoriasis.

Like tyloma, heloma are essentially epidermal in origin but may become more complex because of alteration in the dermis and a source of considerable intractable chronic pain. This is due to the imbalance created in the normal chemo-epidermal function and the development of hyperkeratotic lesions with neural and vascular components, many times encapsulated, giving rise to significant pain and discomfort. The resulting neurovascular lesion, heloma neurovarsculare signifies a long-standing lesion. They result from improper and inappropriate treatment, repeated self-treatment, resulting in haemorrhage and inadequate follow-up care.

Heloma (corn) may arise anywhere on the skin where a bony prominence provides resistance to external pressure. The resulting intermittent stress – a combination of pressure, friction, and shearing – provokes changes in the skin. In the elderly, atrophy of soft tissue and a reduction in the fluidity and elasticity of the soft tissues predispose the elderly to the development of these lesions.

Bursae may occur in the tissues adjacent to a heloma. Localized pinpoint lesions, heloma miliare, or seed corns, occur with extreme localization of pressure, joint deformity, spur formation and/or a protruding irregularity in a shoe. Heloma molle or soft corns are located between the toes, and are macerated due to excessive moisture. Their aetiology is usually due to digital compression accompanied by bony abnormality and/or digital deformities, such as hammertoes and/or rotational deformities. Management in the elderly is essential to prevent infection, particularly from improper débridement. Atrophy of soft tissue and localized pressure lead to keratotic lesions that become chronic and intractable.

Management includes initial débridement, the use of emollients such as 20% urea or 12% ammonium lactate, and procedures and materials to reduce pressure. Silicone moulds to compensate for deformity, padding materials to provide weight diffusion, orthotics to provide stability and weight dispersion, and shoe modifications as needed are also considerations in a long-range approach to the management of these lesions in the elderly. Surgical repair should be considered when indicated.[10]

Ulcers

Diabetes mellitus, peripheral vascular insufficiency, and repetitive trauma are the primary aetiologies in the development of ulcerations in feet. A resolution of the ulcer can be maintained with periodic assessment and management and addressing the underlying cause.[11]

Diabetic ulceration commonly occurs on weight-bearing areas of the foot. The tissues overlying any bony prominence exposed to repetitive pressure may also breakdown and ulcerate. Even bed-ridden patients may develop ulcers due to the weight of bedclothes or that of one limb upon another. Diabetic ulcers may involve deeper structures. Surgical intervention may be required; débridement, drainage and possible skin grafting. The use of contact casts or removable cast walkers can be considered, but the patient's ability to adapt to these ambulatory changes must be part of the consideration for their use.[12,13]

Ulcers that are due to arterial insufficiency are usually very painful and present with pending necrosis and gangrene. The ulcer is usually dry and at some point, the decision to manage and/or amputate will require consideration. The decision should be based on the clinical presentation and the needs of the patient.

Ulcer aetiology and assessment are initial considerations. Location, wound size and shape, wound bed, colour, drainage, wound edges, pain, periwound area, odour, oedema and the signs of infection are important issues. Management includes removing devitalized tissue by débridement (mechanical and/or chemical), autolytic enzymes and appropriate dressings. The potential for infection is a critical issue, requiring early management. Preventing local injury and supporting the repair process are equally important. Vascular complications require indicated consultations and possible surgical intervention. Topical recombinant platelet-derived growth factors can assist in wound care. Continuing evaluation, local wound care, management and prevention are continuing issues, particularly in the older patient.[14]

Management should also include relief of pressure, control of infection and appropriate débridement. Note should be made of the duration of the ulcer, size of the ulcer, depth of the ulcer, and the amount of necrotic tissue present. Treatment parameters also include assessment of the patient's mental status, mobility, infection, tissue oxygenation, chronic pressure, arterial insufficiency (small vessel ischaemia), venous stasis, oedema, type of dressings and chronic illnesses such as diabetes mellitus, uraemia, COPD (chronic obstructive pulmonary disease), malnutrition, CHF (congestive heart failure), anaemia, iron deficiency and immune deficiency disorders. In addition, signs and symptoms, other medical conditions, the wound status, the patient's response to treatment, and early consultation are also important factors to preserve the patient's limb and life.[15]

Toenails

As appendages of the skin, toenails very readily reflect its state, becoming hard, dry and brittle as age advances. Not infrequently, the nail plate is thinner than usual due to atrophy. In other instances, the toenails become so thickened and deformed that the patient cannot cut them and they are ashamed to show their nails to another person. The resulting discomfort may prevent them from wearing any other footwear than a house slipper, making the patient housebound. In addition, the deformity may present a podalgic gait and produce a degree of ambulatory dysfunction, making the patient partially functionally disabled and at risk for a fall.

Trauma is a precipitating factor in the development of thickening of the nail plate. The trauma may have been acute and marked or may be chronic and minimal, such as the constant friction or impaction of the toenail against the inner portion of the toe box of the shoe. The nail plate may grow and twist across the foot (onychogryphosis or 'Ram's horn nail') (see Figure 92.6). It also presents as a residual of inappropriate or no treatment. The danger of this condition is that the nail may penetrate the skin and provide a portal of entry for pathogens, resulting in infection.

Toenails sometimes assume a claw-like appearance due to a dramatic increase in the transverse curvature (involution, convolution, or onychodysplasia). They may also become thickened (onychauxis). Unskilled and inappropriate attempts to 'dig out' the corners of this so-called ingrown toenail, because it is painful, very often lead to inflammation (onychia) and infection (paronychia). Temporary relief may be obtained but skin retraction usually

Figure 92.6 Onychogryphosis, onychomycosis, onychodystrophy, multiple hammertoes, soft tissue atrophy, peripheral arterial disease.

results in increased pain and infection a short time after this attempt. Patients who have poor peripheral arterial supply may face serious consequences from the improper management of this condition. Very thin nail plates may also penetrate the skin of adjacent toes, with similar results.[16]

Hyperkeratosis in the nail grooves (onychophosis) or under the free edge of the nail also creates pain. Periodic débridement of the thickness and length of the toe nail then permits débridement of the keratotic tissue. This is achieved with the use of a nail forceps, curette, and drill, and an appropriate burr. Suitable dressings of chamois, leather, ointments, or silicones, such as Viscogel can be utilized as nail packing under the nail plate to prevent it from digging into the surrounding tissue. The use of emollients such as 20% urea or 12% ammonium lactate also helps as a preventive measure. Depending on the patient's general health and the pain and deformity, avulsion of the whole nail or part of the nail plate, under local or regional anaesthesia may be considered.

Another relatively common cause of thickening of the nail plate is mycotic infection. Streaks of yellow or brown discolouration may extend from the free edge, proximally to the lunula. One or more nails are usually involved, become thickened, brittle and produce a characteristic musty odour. The patient's concern may be the unsightly nail that makes a hole in hosiery and sometimes the uppers of their footwear. Pain is associated with deformity. However, this chronic infection may produce a mycotic onychia and may serve as a focus of infection.[17]

The most common organism producing these changes is *Trichophyton rubrum*. Although it is generally confined to the nails, the surrounding skin and interdigital spaces may become scaly and itch intensely. Sometimes the infection spreads more extensively over the so-called moccasin area. Miconazole nitrate is an example of an antifungal agent that is effective in the treatment of mycotic infections of the skin. Oral terbinafine hydrochloride, itraconazole and topical ciclopirox are available for the management of onychomycosis. Forty percent urea gel is also utilized as a topical application to assist in local onychial débridement. The appearance of the nail plate can be improved and the patient's comfort increased by reducing the thickness of the nail plate and providing a smooth surface to the plate.[18–20] Laser application is also being utilized as a part of overall management.

Bursitis

Bursae are found in a number of situations in the foot. The adventitious bursa over the medial aspect of the first metatarsophalangeal joint frequently becomes inflamed when the joint it overlies is deformed and enlarged, as in hallux valgus. Bursae are also found superficial and deep to the Achilles tendon, the plantar aspect of the heel and the lateral aspect of the fifth metatarsophalangeal joint (tailor's bunion). If for any reason, a superficial bursa is ruptured, secondary infection can ensue. A sinus may be formed and chronic subacute bursitis is then a persistent problem.[21]

Enforced rest for long periods due to debilitating illness or accidental injury may lead to laxity and atrophy of the plantar calcaneal fibro-fatty padding, associated with dehydration. The plantar calcaneal bursa is then vulnerable due to overuse. Plantar calcaneal spurs and plantar myofascitis may also become troublesome in these circumstances.[22]

The immediate treatment for bursitis is to reduce the inflammation and to manage any secondary infection that may be present. Pressure on the areas can be reduced with padding and shoe modifications. Physical modalities, such as heat and ultrasound can be of assistance if properly utilized. Local steroid injections and the use of non-steroidal anti-inflammatory drugs are indicated, when appropriate, in the elderly.[23]

In the long term, stress on the bursae has to be reduced to minimize an exacerbation of the condition, once the acute symptoms are resolved. This may involve modification to footwear and/or the wearing of an appropriate shield (orthotic), such as a silicone mould. Plantar bursitis, with fasciitis and calcaneal spurs, can be improved with the use of heel cups, silicone heel pads, and/or orthosis that provide weight diffusion and modify the weight/pressure relationships in a superior, lateral and posterior direction. Insoles from Plastazote, PPT and other similar materials can aid in weight diffusion and dispersion. The normal warmth of the foot, even in the geriatric patient, will help mould the Plastazote. The resulting wear marks can be a good guide when constructing a more durable orthotic from materials such as Vitrathane. Plastazote as an insole or lining material in combination with Vitrathane will relieve the patient of the feeling that they are walking on pebbles, which is the result of soft tissue atrophy and atrophy of the plantar fat pad.

Scarring

Scarring of the plantar surface of the foot may result from accidental injury, for example, penetration of a foreign body, when walking barefoot. It is not infrequently iatrogenic in origin, that is, following surgery. The plantar metatarsal is the most common site for painful scars on the foot, which in the geriatric, is already deficient in fibro-fatty padding. This can be completely disabling. Patients will require primary podiatric care to débride the keratotic lesions that usually develop within the scar tissue. Appropriate orthotics and insoles as noted above, should be employed to reduce friction and pressure by weight diffusion and dispersion.

Fissures

Fissures will frequently penetrate the underlying dermis and provide a portal of entry for pathogens. Soft tissue haematoma is also a pre-ulcerative state. In the geriatric, stress marks along the outer portion of the heel also serve as an aetiological factor and form the initial stages of pressure ulcerations. Fissures around the heel are usually dry and vertically oriented. Secondary infection is always an added risk. Interdigitally, fissures are usually moist and follow the flexures of the skin. Infection of the interdigital fissures may penetrate the fascial planes and require surgical drainage. The edges of the fissures usually become hyperkeratotic and indurated in the elderly patient, which prevents healing and can be extremely painful.

Moist fissures respond well to antiseptic dressings and if required, antifungal agents. When healed, follow-up skin care is essential. The hard edges of the dry fissures should be débrided. This may be aided by the use of 12.5% salicylic acid in collodion. Its action is to soften the hyperkeratosis and make débridement easier and less painful for the patient. Tissue stimulants can also be employed, once débridement is completed. Bland emollients that help soften keratosis and maintain skin integrity can also be suggested, such as 20% urea creams and 12% ammonium lactate lotion, in addition to daily hygiene.

Management considerations

Since healthy feet are essential for mobility and independence, as well as a catalyst to maintain patient dignity, none who are concerned with health and well-being of older persons should disregard foot care. The particular knowledge and skills of the podiatrist are vital for the multidisciplinary team caring for the geriatric patient. Regular assessment and inspection of the feet are an effective means of monitoring the preventive aspects of the complications of diabetes mellitus and arthritis for example. Other symptoms and overt abnormalities are many times detected during a foot evaluation, with appropriate referral for care to justify the secondary preventive aspects of chronic disease. Periodic evaluation also provides an appropriate time for health education.[24–26]

The following elements are suggested delivery of podiatric care in ambulatory settings, hospitals, long-term care facilities and related programmes:

- Pain should be explored to its fullest extent with all appropriate diagnostic modalities utilized.
- Appropriate, specialized medical consultation is to be employed when indicated. When the diagnosis is in doubt, systemic disease is present and contributing as a complicating factor, then clinical care should be interdisciplinary in approach and based on total patient need.
- Appropriate diagnostic tests should be available and employed when indicated.
- Débridement, pathomechanical, foot orthopaedic, biomechanical, radiographic, orthotic, dermatological and surgical procedures must be applied as elements of total patient care.
- Appropriate pharmacology must be utilized in accordance to local policies and privileges, and the provisions and Drug Enforcement Administration.
- Corrected footwear and orthotics are to be programme components.
- Biopsy and guidelines for follow-up of potential malignancies must be considered and provided.
- Onychial care is to be provided in a suitable manner with consideration of the diagnosis and patient outcome projections.
- At-risk patients who have concomitant systemic disease, such as diabetes, are to receive patient instruction and education as part of the patient education programmes.
- Appropriate physical modalities and procedures for primary inflammation of the foot are to be available, and a component of patient management to complement mechanical and orthotic procedures.
- Health education should be utilized for individual patients, in-group educational settings, and as a part of a total interdisciplinary approach to preventive care.
- Podiatric surgical care is to be in accordance to individual delineation, local facility admitting privileges, and performed in the appropriate setting, utilizing suitable anaesthesia services for patient care.

Foot care

Advice regarding foot care for patients will benefit all elderly people whatever their state of general health. There are a number of excellent publications, available on the Internet, which can be duplicated for patients. Examples include the following:

Nation Institute on Aging – Age Page – Foot Care
American Podiatric Medical Association – Foot Health and Aging
The British Chiropody and Podiatry Association – Foot Care for the Elderly
Public Health Agency of Canada – Foot Care Info-sheet for Seniors
American Geriatrics Society – Aging in the Know – Foot Problems and The Diabetic Foot
American Diabetes Association – Preventive Foot Care in Diabetes
Merck Manual of Geriatrics – Foot Disorders
Pennsylvania Department of Health – Feet First, If the Shoe Fits, and
Assessing the Older Diabetic Foot

These documents plus those listed in the references of this chapter provide a significant amount of information

for professionals and patients which can be applied to the care of older patients for ambulatory care, hospitals, long-term care facilities as well as community and public health programmes.[27]

Footwear

The treatment and long-term management of foot morbidities requires consideration that the foot must be adequately accommodated in proper footwear. The shoe or boot must have adequate width, depth, last and length, especially in the region of the toes. A lace-up shoe reasonably ensures that the foot and shoe are held in the correct relationship as well as having the added virtue that the lace is infinitely adjustable – important where the foot may enlarge because of oedema. The extra depth or super depth shoe is such an example. A surgical shoe or walker is ideal when specific dressing changes are required. High arched feet do sometimes have difficulty with a high lacing shoe. Here a slip-on shoe with an elasticized gusset may be more acceptable. An alternative may be a Velcro and loop closure or elastic laces. This is also useful when the patient is unable to tie his/her shoes. A broad heel with a maximum height of 1.5 in (38 mm) will provide stability. The flaring of the heel on one side or the other to further enhance stability and balance.[28]

The upper of boots or shoes should be plain – devoid of fancy stitching or designs, which involve the overlapping of several pieces of the upper material. These all limit the 'give' of the material and the footwear fails to mould and accommodate minor foot deformities, such as hammer toes and bunion deformities (Figure 92.7).

Traditionally, leather has been the best material for the uppers of footwear, but very satisfactory manmade materials can provide lighter and economical made-to-measure footwear for patients with feet deformed by disease or altered in shape as a result of surgical intervention.

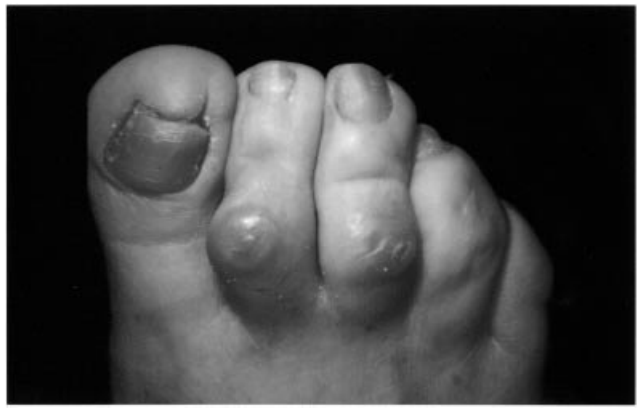

Figure 92.7 Multiple hammer toes, heloma durum, onychodysplasia, onychauxis, onychophosis.

Synthetic materials used for the sole and heels of modern footwear have good wearing qualities. Their thickness provides a surface that is shock-absorbing and insulating. Modern manufacturing processes easily produce shoes that are relatively waterproof. Flexion of the first metatarsophalangeal joint can be limited by the addition of a steel splint or rocker sole. This can also be helpful in the management of osteoarthrosis of the first metatarsophalangeal joint or in incipient rigidity of this joint. Patients should be encouraged to keep all footwear in good repair. Serious injuries to the ligaments of the ankle and subtalar joints are frequently the result of badly worn heels.[29–31]

Orthotics

The prolonged application to the foot of adhesive pads and dressings is undesirable, even with modern hypoallergenic adhesives. It is also aesthetically unacceptable. The warmth and moisture resulting from occlusion of the skin may provoke contact dermatitis or infection, particularly in the elderly. Because of the fact that for many elderly patients, correction or cure is not possible, comfort becomes a primary goal. Deformities may need to remain but care should be directed to relieving pain, restoring a maximum level of function, and maintaining that restored degree of pain-free activity. Many forms of orthotics are available including silicone moulds, soft, rigid or semi-rigid devices. Others include devices that can be made to prescription and fabricated from manmade materials of varying thickness and density. Thermoplastic materials may be combined in one orthotic to give cushioning or support or redistribute the pressure load. These are all fabricated to meet the individual needs of individual patients and the presenting condition. The resulting appliance is more desirable and aesthetically more pleasing since it can be removed, cleaned and utilized in many pairs of footwear.

Where patients are unable to fit and remove these devices themselves, relatives or neighbours can help. A moulded shoe, made from light microcellular material and able to accommodate the most bizarre deformities is the only other alternative, if need be. Sandals or a surgical shoe may be a satisfactory alternative also, where the condition and climate are suitable.

Gels

Whilst podiatrists are familiar with silicone pastes which, by the addition of an activator can be moulded to the unique requirements of individual patients, the resulting orthosis can be bulky and not very resilient. An alternative is to use pre-moulded props, toe separators and toe caps incorporating gels, all of which are washable. Gels are medical-grade mineral oil thermoplastic elastomers from which mineral oil is continually exuded, thus improving the condition of the skin.

Knitted tubing of various diameters, lined with a gel coating is available. This can be cut to the required size. There are also toe caps of various sizes without the knitted cover. Sheet material, 2 mm thick, may be cut to size. Gels may also be incorporated into heel cups and wedges and other types of orthotic to provide 'soft spots' to relieve heel spurs for example. Socks and anklets incorporating gels are also available. These can help in moisturizing atrophic skin and compensating for the loss of subcutaneous soft tissue. They may also be helpful in the treatment of heel fissures and bed sores.

Key points

- Podogeriatrics is that special area of podiatric medical practice that focuses on health promotion, prevention and the treatment and management of foot and related problems, disability, deformity and the pedal complications of chronic diseases in later life. The reasons to refer patients for podiatric care include as examples, the following:
  - –Signs suggesting generalized disease that include neuropathy, vascular disease infection, etc. and focal neoplastic disease;
  - –In those cases where concomitant therapy is indicated;
  - –Where initial management is not effective;
  - –In the presence of skin, nail, postural and joint deformities of the foot and related structures;
  - –In the presence of diabetes mellitus, neurosensory, peripheral
  - –vascular and other risk diseases;
  - –In the presence of foot problems combined with walking problems and/or a history of falls;
  - –Where orthotics are indicated;
  - –If the patient is unable to obtain and/or provide foot care;
  - –If the patient complains of a foot problems or has specific questions about care including information on footwear.
- Foot problems are common in the older population as a result of disease, disability, deformity and complications related to multiple chronic diseases. They also result from neglect and a lack of preventive service, at the primary, secondary and tertiary levels. Foot problems contribute to disability and can reduce an older person's independence and quality of life.
- Because of the risk involved in the geriatric patient and the relationship to multiple chronic diseases, assessment, examination and evaluation of the feet of the elderly is critical. Essential as elements of this process include needs, relationships to ambulation and activities of daily living, instrumental activities of daily living, and the fact that foot pain can result in functional disability, dysfunction, increased dependency, limit mobility and prevent older individuals to live life to the end of life.

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CHAPTER 93

Hip fracture and orthogeriatrics

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Background

In the elderly population, hip fracture is the most common cause of unplanned admission to an acute orthopaedic ward[1] and the second cause of hospital admission in general. The incidence of such fractures has been constantly increasing over the last 70 years and, if we are to believe the demographic projections, it will increase even further. The overall number of fractures, which was 1.6 million per year in 1990, should reach 4 million in 2025 and 7–21 million in 2050.[2] This 'orthopaedic epidemic' raises major medical, economic and social problems and is a challenge in terms of public health, if we wish to promote prevention and develop the least costly and most effective mode of management.

The risk of hip fracture increases exponentially from the age of 60 and 75% of these fractures occur in women, who are at greater risk because of their longer lifespan and high prevalence of osteoporosis. Femoral neck fracture has many causal factors, associating osteoporosis and falls, the prerogative of 'frail'≫ subjects. It is a hallmark of ageing, as it primarily affects persons with the highest comorbidity (29% have respiratory disorders, 55% have dementia and 68% have cardiorespiratory diseases), who make the greatest demands on home care structures and the most use of walking aids. Nursing home residents are three to four times more likely to be affected as they combine several risk factors (advanced age, low bone mass, impaired mobility, cognitive disorders).

In spite of advances in surgery, anaesthesia and rehabilitative management, hip fracture still has a poor vital and functional prognosis. Depending on the studies, mortality ranges from 5 to 10% in the first month and one-third of elderly patients die within 1 year of fracture, whereas the expected annual mortality in a population of the same age is 10%.[3] These figures have not changed for over 20 years. However, only one-third of these deaths are directly attributable to the fracture and in the remaining cases comorbid disorders are the explanatory factor. The criteria of poor prognosis are advanced age, male gender, poorly controlled comorbid conditions, cognitive disorders, low autonomy and institutionalization.

Proximal femoral fracture is a turning point for the worse in the life of the elderly person and it often leads to loss of independence and social decline, marked by admission to an institution. Only half of patients regain their earlier walking ability. The factors of a good functional prognosis are the absence of cognitive disturbances, the ability to walk unaided with a device prior to fracture, rich social contacts and pursuit of an activity outside the home. About 10–20% of patients remain dependent for their activities of daily living (ADL) and must be placed in a nursing home.

The costs relating to management of femoral neck fracture are high because of the length of hospital stay (2–5 weeks) and the costs incurred for subsequent care due to dependence. According to Dolan and Torgerson,[4] they reach £20 000 for the first 2 years.

It therefore seems necessary to reflect on multidisciplinary management as soon as the patient is admitted and on the implementation of surgical and rehabilitative strategies that are adapted to the elderly person's specific needs if we wish to improve the outcome of these patients, who will be increasingly numerous due to lengthening life expectancy.

Diagnosis and classification

Usually, the diagnosis of hip fracture poses few problems. After a fall from a standing position, the patient complains of pain causing functional disability. A characteristic deformity is observed, associating shortening and external rotation of the leg. Inability to raise the heel above the bed surface with the leg extended is a suggestive sign.

Diagnosis is confirmed by radiography. Anterior images of the pelvis should be obtained with the lower limbs in 10° internal rotation, with a lateral view and sometimes a third anteroposterior view centred on the affected hip in 10° internal rotation.[3] However, it is often not easy to obtain

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satisfactory images because of the patient's pain. In difficult cases, where there is a discrepancy between X-ray and clinical findings, fracture can only be excluded by radioisotope bone scan or magnetic resonance imaging (MRI) (the investigation of choice for non-displaced fractures). Bone scan seems to be less informative in this context, but it is easier to obtain within the short time needed for rapid initiation of treatment.

The radiological investigations allow the classification of the fractures according to the location of the fracture line and the degree of displacement, on which the choice of treatment depends. An anatomical and pathophysiological distinction is made between intra- and extracapsular fractures, whose prognoses differ (Figure 93.1).

Intracapsular fractures (45%) lie between the femoral head and the trochanters within the capsule, whether this is intact or not. They can lead to high-pressure haemarthrosis if the capsule remains intact after injury. These fractures may be displaced or non-displaced. The predominant risk is necrosis of the femoral head, secondary to vascular damage. The arterial branches that feed the femoral head are at risk of being lacerated or stretched by the displacement or may also collapse because of the increased pressure due to accumulation of blood caused by haemarthrosis in an intact capsule.

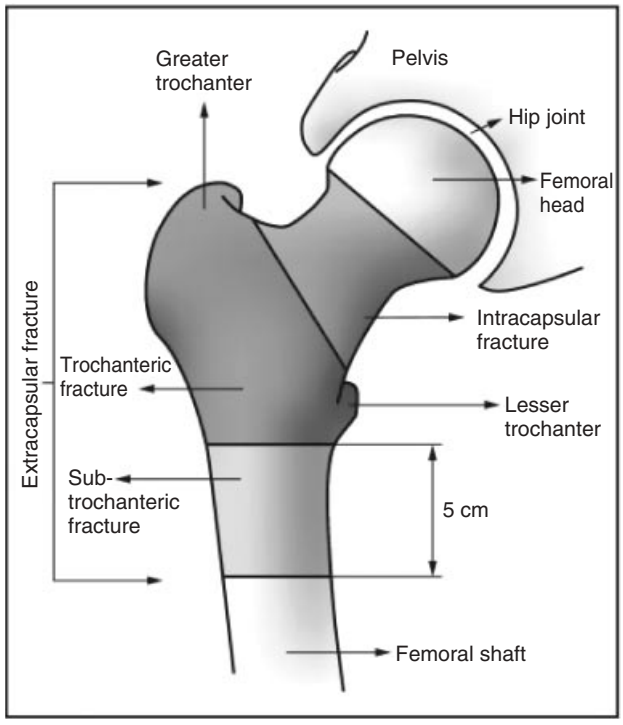

Figure 93.1 Classification of hip fractures by Parker and Johansen. Reproduced from Parker and Johansen,[1] with permission from BMJ Publishing Group Ltd.

Extracapsular fractures are metaphyseal fractures that always heal. They often lead to major bleeding. They are divided into two groups:

- fractures of the greater trochanter (45%), which are stable if there is a single fracture line and unstable if there are several lines
- subtrochanteric fractures (5–10%), which lie within 5 cm distal to the lesser trochanter.

Preoperative care

Analgesia

There is now a general consensus that pain needs to be managed in the emergency situation. Relief of pain reduces the neuroendocrine disturbances that follow the trauma, decreases the patient's agitation that can lead to secondary displacement of the fracture site and makes preoperative investigations easier. Pain is judged by repeated self-assessment. A simple verbal scale (from 0, no pain, to 4, extreme pain) is preferable to the visual analogue scale in the elderly person, who may find it difficult to cooperate.

In general, level 1 analgesics (paracetamol) used alone do not adequately relieve pain. They should be prescribed in association with a level 2 analgesic (codeine) or a morphine derivative. As a parenteral approach is often necessary, the dose of morphine derivatives must be carefully titrated in these frail patients. Non-steroidal anti-inflammatory drugs (NSAIDs) are inadvisable in the elderly patient as the risk of haemorrhage is increased by stress and because of pre-existing renal failure.

Peripheral blocks have considerably improved pain management in femoral neck fractures. An iliac fascia block carried out as soon as the patient has been admitted to the emergency department allows them to be mobilized and prepared for surgery.

Preoperative traction

Both skin and skeletal traction have been proposed in order to reduce pain and to facilitate fracture reduction. However, the studies available[5] have not provided sufficient evidence of sedation of pain in the first 2 days after surgery {relative risk (RR) = 1.14 [95% confidence interval (CI), 0.89–1.46]} and RR = 1.02 (95% CI, 0.74–1.41)] or of easier fracture reduction at the time of surgery.

Electrolyte balance and blood transfusion

In the elderly person with hip fracture, *electrolyte imbalance* is frequent and due to a variety of causes, such as renal failure, diabetes and diuretic medications. Patients are often dehydrated, either because they lay on the ground for several hours or because of preoperative fasting.

These imbalances should be corrected, while taking into account the borderline tolerance of volume restoration in elderly patients.

Anaemia, particularly frequent in fractures of the greater trochanter, increases the mortality rate at 6 and 12 months, lengthens the duration of hospital stay and compromises the functional prognosis.[6] The transfusion threshold is still difficult to establish, but it is generally accepted as 8–9 g dl^{-1} for elderly patients with no cardiovascular history and 10 g dl^{-1} for patients with poor tolerance or severe cardiovascular involvement.

Thromboembolic prophylaxis

Following proximal femoral fracture, the risk of thromboembolism is increased. The incidence of proximal thrombosis is 27% and mortality due to pulmonary embolism is 1.4–7% in the first 3 months after surgery.[7] In view of these figures, the absence of thromboprophylaxis may be considered as negligence. A Cochrane review of 31 studies (2858 participants) clearly demonstrated the efficacy of prophylactic treatment in reducing the incidence of deep venous thrombosis (DVT) and pulmonary embolism.[8] The modalities of management, however, still remain to be defined: the respective roles of pharmacological and physical methods, optimal duration of treatment. Several therapeutic protocols are under discussion:

- Administration of unfractionated heparin or low molecular weight heparin versus placebo (15 trials, 1199 participants) significantly reduced the risk of DVT [RR = 0.60 (95% CI, 0.50–0.71)], but evidence regarding pulmonary embolism was inadequate. Low molecular weight heparins were not more effective than fractionated heparins.
- Low-dose aspirin appears likely to decrease the incidence of DVT and pulmonary embolism.
- Antivitamin K agents may also be given during the first 10 days after surgery if a target international normalized ratio (INR) of 2.5 (min.–max. 2.0–3.0) is maintained.

However, we need to be aware that use of anticoagulants or antiplatelet agents increases the number of haemorrhagic complications.

The optimal duration of treatment[9] is still unclear. In general, it is continued for 14 days after surgery. The Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy[10] recommended that heparin should be given for at least 10 days after surgery. However, it has been demonstrated that even with anticoagulation treatment, thrombosis occurs in 15–30% of patients at discharge and that 10–25% of patients develop thrombosis 3–4 weeks later; these thromboses are symptomatic in less than 10% of cases. Eriksson and Lassen[11] showed that 4 weeks of heparin treatment reduced the incidence of pulmonary embolism compared with 1 week of treatment.

When surgery is deferred, initiation of anticoagulation treatment is recommended between admission and the surgical procedure.

Physical treatments have also been proposed. Mechanical pumping devices are more effective than no treatment [RR = 0.31 (95% CI, 0.12–0.51)] and they significantly reduce the risk of DVT and pulmonary embolism, but skin abrasions have been reported.[8] As for compression stockings, it is difficult to reach a conclusion regarding their efficacy.

Lastly, it is important to note that no method makes it possible to reduce the number of fatal pulmonary embolisms, or the mortality after hip fracture.

In addition to specific treatments, it is therefore important to give a considerable place to general measures[1] such as:

- combat against dehydration and excessive transfusion
- minimization of surgical delay and duration of the procedure
- early mobilization of the patient.

Minimizing surgical delay

The Royal College of Physicians' guidelines[12] recommend early surgery (within 24 h of admission). However, after analysis of 10 studies with a satisfactory level of proof, Beaupre *et al*.[7] emphasized that divergent results were obtained when surgical delay was taken into account. With regard to post-surgical mortality, Grimes *et al*.,[13] after adjustment for comorbid conditions, observed no differences between patients operated on after more that 96 h and those operated on within 48 h [HR = 1.01 (95% CI, 0.95–1.21)]. Conversely, Shiga *et al*.[14] carried out a meta-analysis of five prospective and 11 retrospective studies which showed that operative delays of more than 48 h increase 30 day mortality by 41% and mortality at 1 year by 32%. Excess mortality is particularly high in patients aged <70 years with no comorbid conditions. Most authors[15,16] agree that early surgery decreases the risk of postoperative complications such as pressure ulcers, urinary infections, thromboses and pneumonia, but that it sometimes increases the risk of postoperative bleeding and prosthesis-related complications.[16] Several authors also report that early surgery shortens hospital stay,[15] encourages earlier resumption of walking and reduces pain.

These arguments favour early surgery for younger, clinically stable patients. In other cases, it is important that existing comorbidities should be rapidly controlled before considering surgery.

Prevention of pressure ulcers

Following hip surgery, 10–40% of patients develop a pressure ulcer. This complication increases the burden of care, risk of nosocomial infection and duration of hospital stay. The heel is particularly at risk due to increased pressure

on the operated side (immobility of the patient) and on the uninvolved side, because the patient uses the heel as a pivot to move in bed. These mechanical factors are augmented by haemodynamic factors: decreased local blood flow due to elevation of the operated limb during the procedure, fluctuations in blood volume due to anaesthesia and blood loss and sometimes episodes of low blood flow rate related to the cement used in total hip replacement. In these circumstances, bilateral pressure ulcers are observed.[17]

Two studies[7] assessed the preventive efficacy, in orthopaedic surgery, of foam or dynamic air mattresses and showed that their use reduced the incidence of pressure ulcers [RR = 0.34 (95% CI, 0.14–0.85) and RR = 0.20 (95% CI, 0.009–0.45)]. These means of prevention are effective above all for the sacrum and trochanter. A meta-analysis[18] exclusively centred on the prevention of heel ulcers showed that special foam or dynamic air mattresses were superior to standard hospital mattresses. With regard to heel pads and mattress overlays, the evidence was inadequate to reach a conclusion regarding their efficacy.

Overall, rational use of preventive aids (mattresses, heel supports, mattress overlays) is recommended based on evaluation of the patient's risk level using specific scales (see Chapter 126, The prevention and management of pressure ulcers).

Fracture repair and perioperative care

Surgical management

The majority of hip fractures are treated surgically, although conservative treatment, used before the advent of the first prostheses, may still be debated.

Conservative or operative treatment

Handoll and Parker, in a Cochrane review of five randomized trials (428 elderly subjects), compared surgical treatment and conservative treatment (traction and bed rest).[19] A study of 23 patients with non-displaced intracapsular fractures showed a lower risk of non-union in surgically treated patients. The other trials relating to extracapsular fractures found no difference in mortality, medical complications or pain between the two treatment modalities, whatever the prosthesis or surgical technique used. However, deformity and limb shortening were less frequently observed with surgical treatment (better anatomical reduction), duration of hospital stay was shorter and functional results were better. Conservative treatment should be the exception today, reserved for patients with formal contraindications to surgery, those who refuse it or those who are at the end of life.

Operative treatment

Undisplaced intracapsular fractures

Only internal fixation is recommended, as it reduces the risk of displacement. The surgical procedure is simple and can be carried out by a percutaneous approach under local anaesthesia or peripheral block. Two or three screws are used in parallel (Figure 93.2) or a sliding hip screw (SHS). This technique has the advantages of being conservative and of making nursing care easier. Active mobilization of the hip and knee can rapidly be started.

Displaced intracapsular fractures

Two options are possible: internal fixation or prosthetic replacement. Each treatment carries specific complications.

Internal fixation is a shorter procedure, with less blood loss and less risk of infection; the main complications are non-union and avascular necrosis of the femoral head, requiring revision in 35–50% of cases.

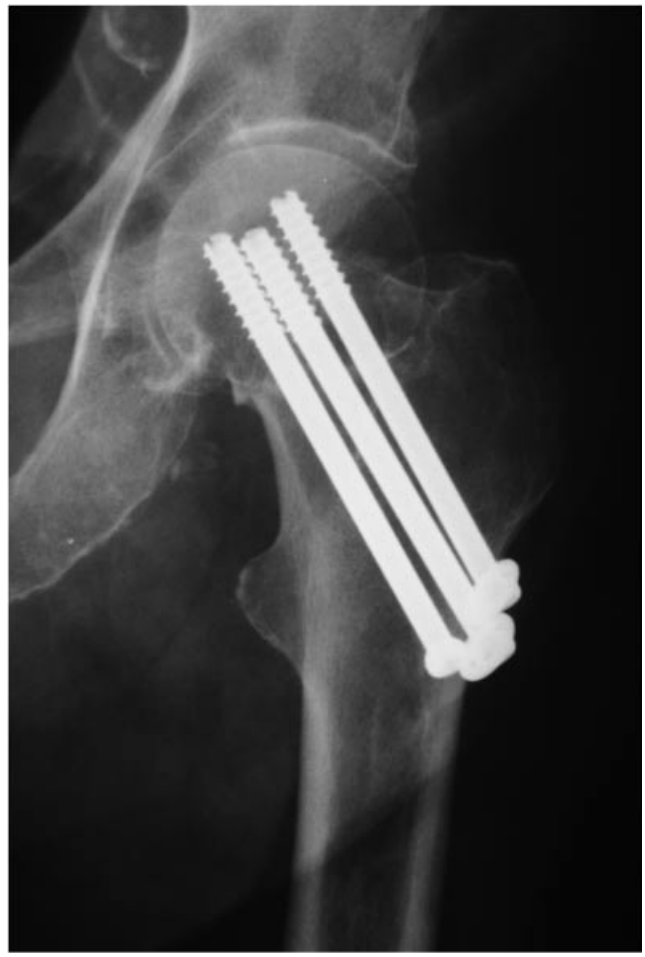

Figure 93.2 Intracapsular fracture fixed with three screws.

Several types of prostheses may be used:

- Cervicocephalic hemiarthroplasty prostheses (Figure 93.3) of Moore or Thompson type replace only the femoral head. They are non-cemented and are inserted as a press-fit in cancellous bone.
- Bipolar hemiarthroplasty prostheses (Figure 93.4) have a femoral part with a mobile acetabular socket joint which is intended to protect the acetabulum and to delay the development of mechanical complications.
- Total prostheses (Figure 93.5), very widely used in the surgical treatment of coxarthrosis, replace the entire coxofemoral joint.

Prostheses may be cemented or uncemented. Randomized trials comparing cement with cementless devices are summarized in a Cochrane review.[20] Cemented prostheses are less painful and the functional results are better, but with the drawback of a more lengthy and major surgical procedure (risk of cardiovascular collapse, toxic effects of cement). Mortality is not increased at 1 year.

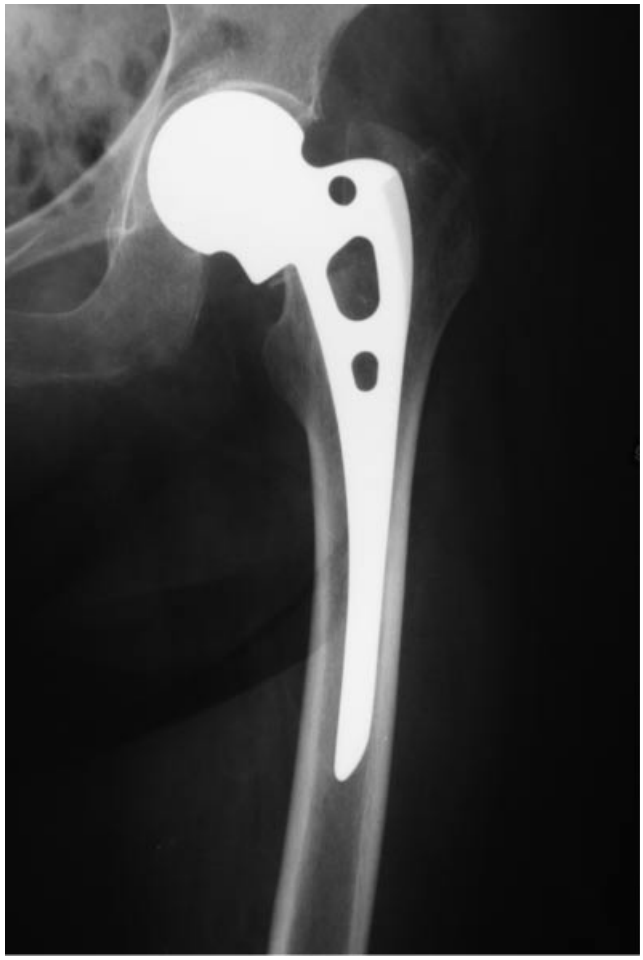

Figure 93.3 Fracture treated with an uncemented Moore hemiarthroplasty.

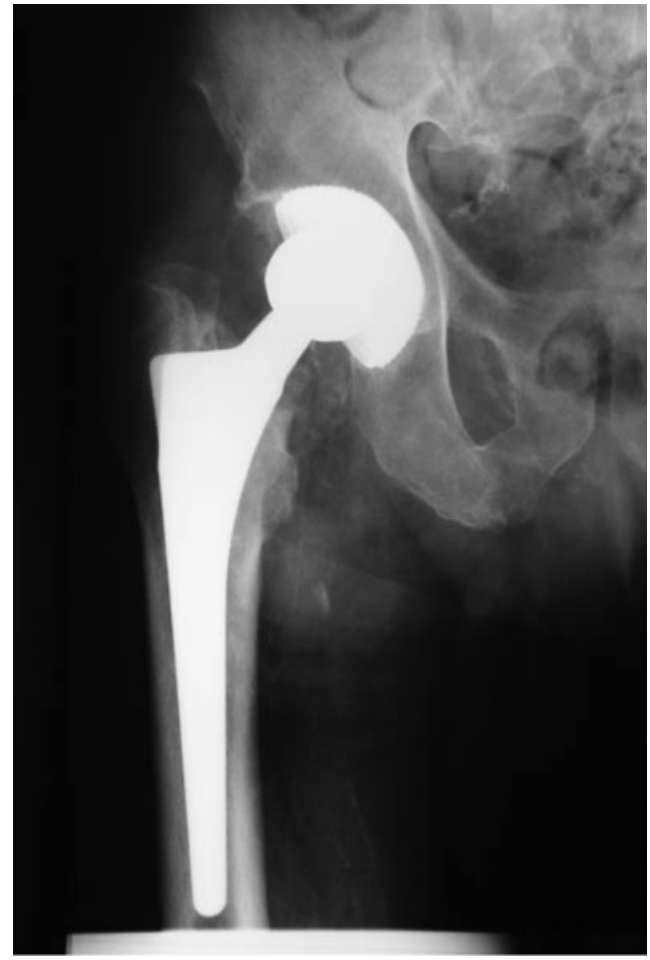

Figure 93.4 Fracture treated with a cemented total arthroplasty.

A Cochrane review compared the two operative techniques (internal fixation and hip replacement) in the adult.[21] The results did not differ in terms of mortality, but postoperative pain was less and the functional results were better after hip replacement. An observational study,[22] based on the Norwegian register of hip fractures and including 1569 subjects aged over 70 years operated on for femoral neck fracture, stressed that patients who underwent bipolar arthroplasty had a better quality of life at 4 months than those treated by internal fixation. They had less pain and were more satisfied with the intervention. Arthroplasty also gives better results in severely demented patients. however, the superiority of prostheses is apparent essentially for the most modern bipolar prostheses (hydroxyapatite) and for cemented prostheses.

In view of these considerations, the choice of operative technique must take into account the age of the patient, risk factors, cognitive state and level of mobility before the accident. It seems advantageous to propose total hip arthroplasty for subjects aged over 70 years who are active and in

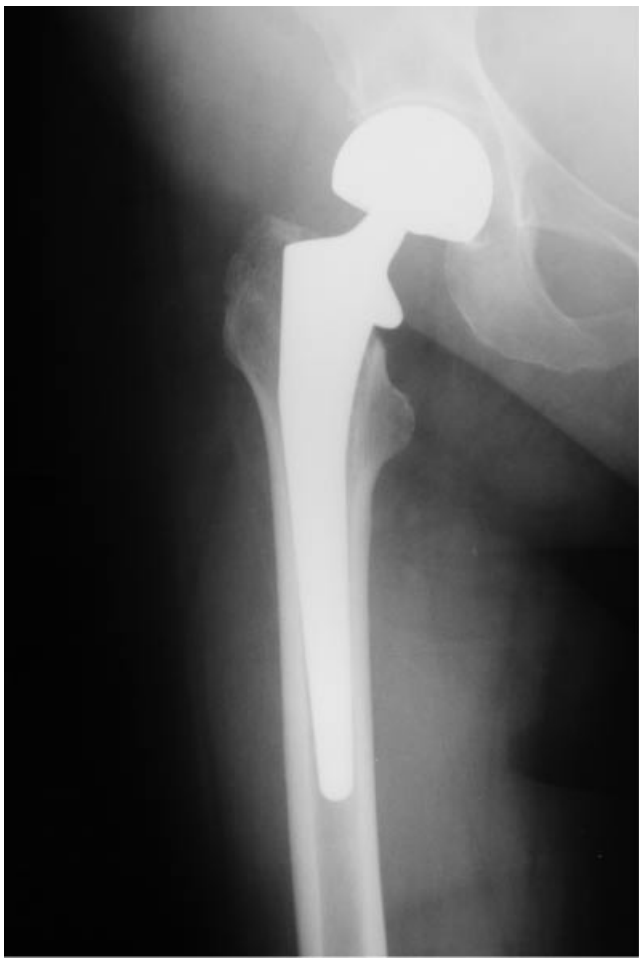

Figure 93.5 Bipolar hemiarthroplasty.

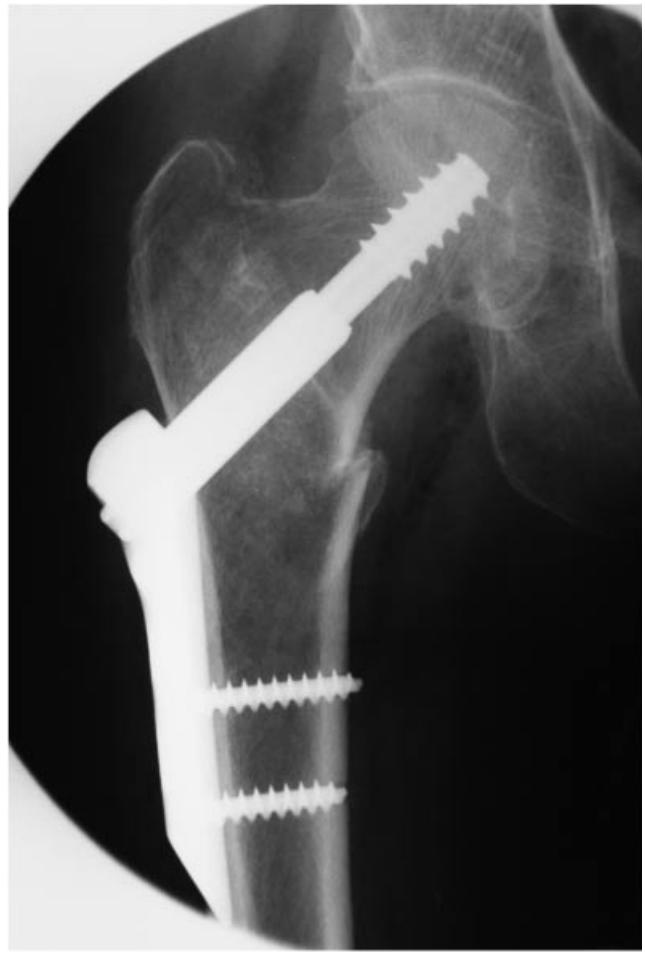

Figure 93.6 Trochanteric fracture fixed by dynamic hip screw.

good health and who still have a long life expectancy.[23] Total hip arthroplasty does not carry a higher risk of displacement.

Trochanteric fractures

Numerous surgical possibilities are available for this type of fracture, although SHS is the gold standard. The implants proposed are dynamic hip screws (DHS) (Figure 93.6), compression hip screws and Ambi screws. Among the more recent alternatives are the gamma nail (Figure 93.7), the intramedullary hip screw (IMHS), the proximal femoral nail (PFN), the Holland nail and the Targon nail. Compared with SHS, they seem to be accompanied by more frequent redisplacement and an increased number of reinterventions.[3] Hip replacement has also been proposed for particularly unstable fractures. A Cochrane review found no difference between hip replacement and SHS for surgical complications, mortality rate or functional results at 1 year.[24]

Subtrochanteric fractures

Stabilization is the main problem with these fractures. The prostheses proposed are SHS or centromedullary nails, with a risk of fracture in the vicinity of the nail stem.

Type of anaesthesia

General anaesthesia increases the risk of postoperative delirium in elderly subjects. A Cochrane review of 22 trials (2567 participants) showed decreased mortality at 1 month with regional anaesthesia (6.9 versus 10%), but these results were of borderline significance, with RR = 0.69 (95% CI, 0.5–0.95). The risk of DVT was also decreased, with RR = 0.64 (95% CI, 0.49–0.92).[25] Another systematic review of 141 studies (9559 participants) also showed lower mortality with regional anaesthesia.[26] Forty-four of these studies (31%) specifically involved elderly subjects and they confirmed that regional anaesthesia reduced the

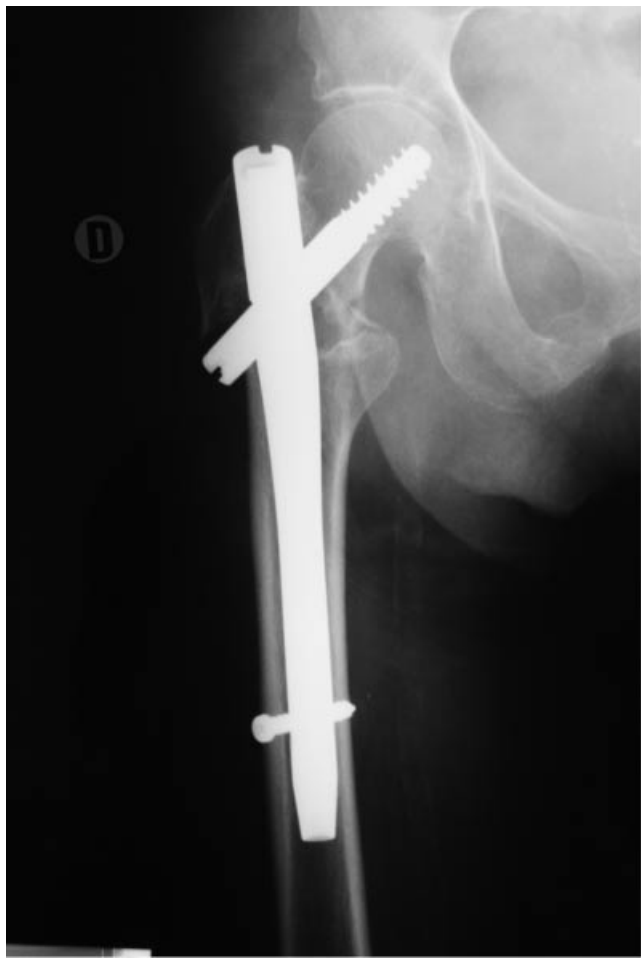

Figure 93.7 Trochanteric fracture fixed by gamma nail.

risk of DVT [odds ratio (OR) = 0.56 (95% CI, 0.43–0.72)], pulmonary embolism [OR = 0.45 (95% CI, 0.29–0.69)], transfusion requirements [OR = 0.50 (95% CI, 0.39–0.66)] and pneumonia [OR = 0.61 (95% CI, 0.48–0.76)]. However, the choice made by the anaesthetist must take into account the preferences of the patient and their family, and also imperatives related to the patient's clinical condition and the operative procedure.

Antibiotic prophylaxis

A meta-analysis of 22 randomized controlled trials (RCTs) (8307 subjects surgically treated for fracture), including 16 RCTs concerning surgical treatment of proximal femoral fractures, showed that antibiotic prophylaxis reduced the incidence of deep infections, with RR = 0.36 (95% CI, 0.21–0.65), and urinary infections, with RR = 0.66 (95% CI, 0.43–1). Results were identical with a single injection of an antibiotic with a long half-life (>12 h, such as cefazolin 1 g) or with multiple injections of antibiotics with a short half-life.[7]

Postoperative wound drainage

Insertion of a drain to prevent haematomas is usual practice in hip surgery, but can also create a portal of entry for infection. In a systematic review of three RCTs (333 participants), it was observed that infections and surgical revisions were not more numerous when a postoperative drain was placed and that the drain did not increase the risk of bleeding.[7]

Urinary tract catheterization

Following hip surgery, the incidence of urinary infections is 23–25%. In spite of the frequency of this complication, there have been few studies of the modalities and the consequences of catheterization during the perioperative period. Cumming and Parker[27] emphasized a possible relationship between deep infections and prolonged urinary catheterization. In this study, infected patients had been catheterized on average for 6.9 days, compared with 3.5 days for those who did not present this complication. The number of patients who had required a long-term catheter (>21 days) was higher in the infected group ($p = 0.01$). Lastly, multiple catheter insertions were also identified as a risk factor for infection.

It therefore seems reasonable to use long-term catheterization only if the patient has urine retention and to ensure meticulous technique during insertion and care of the catheter (see Chapter 104, The ageing bladder).

Prevention of delirium

Delirium in the elderly person with a proximal femoral fracture is a complication whose prevalence is difficult to determine (5–54.3% depending on the series). The available studies come up against an absence of consensus on evaluation tools and against the difficulty of diagnosis, since fluctuation of the signs is a diagnostic criterion. Delirium is a marker of poor prognosis and is associated with increased morbidity and mortality, longer hospital stay and the risk of institutionalization. It also increases the cost of management.

Juliebo *et al*.[28] identified the risk factors for preoperative delirium as cognitive impairment, indoor injury, fever and operative delay, and for postoperative delirium as cognitive impairment, body mass index <20 and indoor injury. The pathophysiological mechanisms of delirium in this setting are poorly known, but either cholinergic deficiency or an inflammatory process have been suggested. Patients treated with statins appear to be protected to some extent, perhaps because of the anti-inflammatory action of these drugs. The prognosis is worse if delirium is associated with dementia or a depressive syndrome. Reliable studies on means of prevention are lacking. A Cochrane review

analysed six studies (833 participants) on postoperative delirium, of which five related to orthopaedic surgery.[29] A single study (126 patients) involved elderly subjects who had had surgical treatment for hip fracture. It found that a preoperative geriatric consultation effectively reduced the incidence of episodes of delirium and suggested that treating 5.6 patients resulted in the prevention of one case of delirium. This type of intervention seems particularly effective in preventing severe forms, but it does not influence duration of delirium or duration of hospital stay, cognitive status or rate of institutionalization at discharge. Another study emphasized the efficacy of low-dose haloperidol in reducing the severity and duration of these episodes and in shortening hospital stay.

Postoperative care

Early mobilization and weight bearing

Postoperatively, when the patient's clinical condition has been stabilized, all efforts are directed towards rehabilitation. Early mobilization of the patient is generally recommended to prevent the complications of bed rest. However, in a Cochrane review that included seven trials, Handoll *et al*.[30] did not find a sufficient level of proof to affirm that this approach improved results. With regard to time to resumption of weight bearing, there are no strict rules. After prosthesis insertion, weight bearing is permitted as soon as the patient's clinical condition allows it. For subjects who have had internal fixation, the assembly is in general sufficiently stable to allow partial weight bearing almost immediately, but in elderly subjects this recommendation is purely theoretical and weight bearing is guided above all by pain; there is no significant difference in outcome between subjects who resume weight bearing early or late.

Rehabilitation

Various modalities of rehabilitation have been described in the literature, but the trials are heterogeneous both in the techniques used and in the context and duration of care. The respective efficacy of the protocols is therefore difficult to assess, whether in terms of functional results or of cost.

Multidisciplinary rehabilitation

Multidisciplinary rehabilitation involving physical therapists, occupational therapists, psychologists and social workers, organized by a physician around a common objective, was the basis of several studies discussed in a Cochrane review.[31] The cumulative results of 11 trials showed no superiority of this mode of management in terms of medium-term mortality, patient outcome or number of hospital readmissions. However, some studies taken in isolation show that this method improves functional recovery. Results diverge with regard to duration of hospital stay.

Some authors have looked at the possibility of *rehabilitation at home* and have assessed its efficacy. According to Beaupre *et al*.,[7] multidisciplinary management at home did not lead to greater gains in ADL or IADL than conventional physical therapy, although walking ability appeared better in the intervention group. The intensity of exercise was not specified. Giusti *et al*.,[32] in a prospective 12 month study in an unselected population, showed that such an approach was feasible and reported more rapid recovery and better functional results in the group receiving rehabilitation at home.

Intensive rehabilitation

Intensive rehabilitation pursued for a long period after hospitalization has beneficial effects. Mangione *et al*.[33] showed that a 12 week programme after discharge, consisting of either aerobic endurance training or progressive resistance training to strengthen lower limb muscles, resulted in increased walking speed and muscle strength. The increase in strength, however, was greater in the group that underwent high-intensity resistance training. Adherence was 98%.

In a study by Host *et al*.,[34] patients underwent 6 months of rehabilitation (three sessions per week). For the first 3 months the subjects carried out a variety of exercises (suppleness, balance, coordination) and low-resistance muscle strengthening. For the following 3 months, work against resistance was intensified, first to 65% of 1 RM (repetition maximum), then to 85% of 1 RM. This method resulted in significantly increased lower limb muscle strength. The injured limb developed similar strength to the contralateral limb. Functional capacity, walking speed and stair-climbing speed all improved. Two-thirds of patients walked without a cane.

As yet, no method of rehabilitation has really provided evidence of its superiority and so we are unable to propose standardized protocols after treatment for hip fracture. The results largely depend on the patient's abilities and the social context. A personalized approach must therefore be envisaged, while taking into account established prognostic factors such as cognitive status, depression, nutritional status and previous level of autonomy. Based on these criteria, the modalities of rehabilitation may be determined: generally, the most disabled patients are treated in an institutional setting and receive care for a longer period.

Optimizing nutrition

About 30–50% of elderly victims of proximal femoral fracture are malnourished at admission to hospital and this is an independent risk factor of morbidity and mortality. This situation worsens during the perioperative period due to the hypercatabolism related to the stress of injury and surgery. Hypercatabolism persists for 3 months after

surgery and protein and energy intakes are seen to be less than requirements, leading to weight loss to the detriment of lean mass. Interventional studies with the aim of improving the nutritional intake of these patients are numerous, but their methodology is often mediocre.[35] Eight trials assessed the efficacy of protein, energy, vitamin and mineral supplementation and showed that this type of intervention, even if it does not decrease mortality, improves the quality of survival, with RR = 0.52 (95% CI, 0.32–0.84). High-protein diets are likely to decrease long-term complications and to encourage progress in rehabilitation. However, intravenous administration of vitamin B_1 or vitamin D was of no benefit. Recourse to feeding by nasogastric tube must be avoided because of poor tolerance and unproven efficacy.

Conversely, a randomized trial yielded evidence that providing the patient with assistance in order to eat better tended to decrease mortality.[35] This type of approach ensures better compliance and greater patient satisfaction.

Lastly, a randomized double-blind study showed that an intravenous supplement given for 3 days followed by an oral nutritional supplement twice per day for 7 days reduced the number of infectious complications and decreased mortality 3 months postoperatively.[36] However, this is an unusual nutritional protocol whose results need to be confirmed (see Chapter 15, Epidemiology of nutrition and ageing).

Surgical complications

Wound healing complications

The most frequent complication is haematoma (2–10%). The haematoma is generally not abundant and regresses spontaneously, although some cases may require surgical drainage. Superficial infections generally respond favourably to appropriate antibiotics according to bacteriological findings.

Deep infections after hip replacement occur in 0.3–2% of first-time surgical procedures and in as many as 5% of hemiarthroplasties. These complications are severe in frail elderly subjects, leading to loss of mobility and even death (11% at 3 months and 33% at 12 months). The prosthesis has to be removed, definitively compromising walking for the frailest elderly. Deep infection is rare after internal fixation.

Internal fixation of intracapsular fractures

In the weeks following surgery or on weight bearing, redisplacement of the fracture site may be observed or at a later stage delayed union or even non-union. However, the most frequent complication is vascular osteonecrosis of the femoral head. This generally occurs in the first 2 years after fracture and requires insertion of a prosthesis.

Sliding hip screw and intramedullary nail: fixation of extracapsular fractures

This type of internal fixation may be complicated by redisplacement, which requires surgical revision to stabilize the fracture site or by displacement of the cephalic screw, which may perforate the femoral head and impinge on the acetabulum. Some patients complain of pain of the outer thigh due to irritation of soft tissue by the surgical material. This may need to be removed once the fracture is consolidated.

Arthroplasty complications

Dislocation represents 13–22% of early complications, depending on the series, and 32% in patients with cognitive impairment. The incidence can be reduced by training care teams to avoid movements that put the hip at risk of dislocating (Table 93.1) during transfers and by using abduction cushions.

Some time after surgery, pain may develop which restricts walking. It is generally related to acetabular erosion (particularly frequent after Moore hemiarthroplasty), to stem impaction or loosening of the prosthesis. The prosthesis is replaced whenever the patient's condition allows.

Secondary fracture prevention

After proximal femoral fracture, in spite of rehabilitation measures the majority of elderly patients complain of weakness and loss of strength that is greater in the operated leg. This worsens pre-existing disturbances of balance and gait and increases patients' frailty. During the first year after fracture, 56% of subjects have a fall, 28% have repeated falls, 12% present with a new fracture and 5% fracture the opposite hip.[37] The occurrence of a hip fracture therefore necessitates a specific management approach with the aim of reducing the incidence of new fractures. As fracture is the result of the fall impact on bone fragilized by ageing, prevention should centre round three points:

- assessment of risk of falls and development of preventive interventions
- protection of the trochanteric region with hip protectors
- management of osteoporosis.

Table 93.1 Recommendations for avoiding dislocation of a hip prosthesis.

- Avoid movements that increase the risk of dislocation:
  - hip flexion with abduction and external rotation
  - hip flexion with adduction and internal rotation
- Get out of bed on the replacement side
- Do not cross the legs
- Do not squat or sit on too low a chair
- Do not rotate the trunk with the foot on the ground

Falls risk assessment and intervention

In the elderly person, falls are generally the consequence of multiple risk factors and/or risk situations, which can very often be corrected (see Chapter 91, Gait, balance and falls). The modalities of evaluation of fall risk in subjects who have already had a fall are defined in the guidelines of the American Geriatrics Society[38] and the National Institute for Health and Clinical Excellence (NICE)[39] (Table 93.2). It must be stressed that risk increases exponentially when several factors are associated and this has led to the development of multifactorial interventions. In a Cochrane review, Gillespie *et al*. analyzed 62 trials (21 668 participants) and showed, for example, that interventions acting on the environment and state of health are effective in unselected populations [four trials, RR = 0.73 (95% CI, 0.63–0.85)] and also in subjects who have already had falls [five trials, RR = 0.86 (95% CI, 0.76–0.98)] or those living in sheltered housing [one trial, RR = 0.60 (95% CI, 0.50–0.73)].[40] Among the single-factor interventions that have demonstrated their efficacy, we may mention some personalized home-based programmes that combine muscle strengthening and balance training [three trials, RR = 0.80 (95% CI, 0.66–0.98)], the practice of tai chi for 15 weeks, customized safety measures in the home, reduction in psychotropic treatments and pacemaker implants (cardiac pacing) in patients with carotid sinus hypersensitivity. Other interventions, such as adaptation of footwear, prescription of walking aids or correction of visual impairments, have not provided sufficient evidence of their effectiveness.

Table 93.2 Summary of fall risk assessment and appropriate interventions.

Fall risk assessment	Intervention (as appropriate)
Identification of falls history	
Assessment of gait, balance and mobility and muscle weakness	Strength and balance training
Assessment of osteoporosis risk	
Assessment of the older person's perceived functional ability and fear relating to falling	Hazard and safety home intervention
Assessment of visual impairment	Visual correction
Assessment of cognitive impairment and neurological examination	
Assessment of urinary incontinence	
Assessment of home hazards	
Cardiovascular examination and medication review	Medication review and modifications/ withdrawal Cardiovascular disorder treatment

Falls may also be secondary to a malaise and so a medical cause should systematically be sought: postural hypotension, vasovagal syncope, carotid sinus hypersensitivity. The minimum investigations in a patient who falls should include measurement of arterial blood pressure in lying and standing positions and a 12-lead electrocardiogram (see **Chapter** 35**, Cardiac ageing and systemic disorder**).

Hip protectors

The majority of fractures of the upper femoral extremity follow a sideways fall directly on to the greater trochanter. One of the means of prevention proposed is the use of a hip protector, which consists of two rigid shells or foam padding, held in position over the trochanters by pants. The aim of this device is to absorb the shock and disperse the energy to the soft tissues. Numerous designs exist and, in the absence of manufacturing standards, we may suppose that their efficacy varies. Three reviews of the literature were published in 2005–2006, including a Cochrane review.[41] Their conclusions differed little. Hip protectors appear to result in marginally lower fracture incidence in institutions but are found to be ineffective in the elderly living at home. Patient adherence is low owing to the discomfort caused by some devices and also perhaps owing to caregivers' lack of motivation, as their workload is increased by the need to adjust the protector.

A multicentre study cast further doubt on the efficacy of this type of device in an institutional setting.[42] This study included 1042 retirement home residents, mean age 85 years, with a follow-up of 20 months. Each patient wore the hip protector on one hip only, the side being selected at random, and was under their own control. Although adherence was much higher than in previous studies, it was not possible to demonstrate the preventive value of hip protectors in this population.

Osteoporosis assessment and treatment

In the elderly subject, only 3% of hip fractures are pathological (metastasis, myeloma, bone cysts, Paget's disease, etc.), but over half of patients are osteoporotic and almost all have osteopenia. After the age of 80 years, a woman with bone mineral density that is normal for her age has a T-score of–2.5 SD (the definition of osteoporosis). Osteodensitometry for diagnostic purposes alone is thus only indicated in women aged <75 years.

Based on a review of 590 trials, the Division of Rheumatology, University of California at Los Angeles, developed quality indicators for the care of osteoporosis in vulnerable elders, a definition which corresponds to elderly victims of hip fracture.[43]

Hence in a patient who has presented a fragility fracture, it is recommended to obtain a full history of medications

taken (corticosteroids) and alcohol consumption and to request laboratory tests (blood count, liver and kidney function tests, phosphorus and calcium levels, vitamin D, thyroid-stimulating hormone) in order to exclude curable secondary osteoporosis and avoid bone loss. In this population, secondary osteoporosis is infrequent and the dominant cause is hyperthyroidism. Malnutrition, low weight, hypogonadism and hyperparathyroid disorders must also be borne in mind.

Every vulnerable elderly person who has had a proximal femoral fracture should receive treatment to prevent a new fracture.

Pharmacological prevention of hip fracture is debated. Several treatments have been proposed and discussed:

- *Calcium and vitamin D in combination* had a beneficial effect in elderly women living in nursing homes, but in a single study carried out nearly 20 years ago.[44]
- *Bisphosphonates*, which have undergone many randomized trials, all led to a demonstrable gain in bone mass. A reduced number of hip fractures was observed with risedronate, pamidronate and zoledronic acid. These drugs were initially administered daily under stringent conditions so as to obtain optimal absorption of the agent, then weekly or monthly formulae were later introduced which made treatment easier. With this therapeutic class, infrequent gastrointestinal side effects have been described and rare cases of osteonecrosis of the jaw. A once-yearly infusion of zoledronic acid was recently introduced that allows the treatment of patients with poor compliance. This treatment reduces the risk of clinical fracture by 33%, of vertebral fracture by 77% and the incidence of peripheral fracture by 25%.[45] Supplemental vitamin D must be given beforehand. Adverse events have been described: influenza-like syndrome at the first infusion (one in three cases) and a higher incidence of atrial fibrillation than in the placebo group.
- *Teriparatide* decreases in osteoporotic women the risk of a new vertebral or non-vertebral fracture independently of the initial T-score, age and number of fractures. The gain in bone mass is dose dependent.
- *Raloxifene* has not been found to decrease the incidence of femoral neck fractures.
- *Hormone replacement treatment* for the menopause has been judged effective in preserving bone mass and decreasing the risk of fracture in several meta-analyses, in numerous controlled trials and in prospective studies. Some trials report adverse events: breast cancer, cardioembolic disease, cerebrovascular accident, coronary failure.
- *Selective estrogen receptor antagonists* must be avoided after femoral neck fracture because of the increased risk of thromboembolic complications.
- *Strontium ranelate* increased lumbar and femoral neck bone mineral density (BMD) compared with placebo after 5 years of treatment.[46] In a subgroup of women aged >80 years, a decreased number of non-vertebral fractures was observed, of femoral head fractures in particular. Two fatal cases of drug rash with eosinophilia systemic symptoms have been reported with this medication. In addition, precautionary measures must be taken if administered to subjects at risk of thromboembolic disease.

Whatever the treatment chosen, it must be combined with an adequate intake of calcium and vitamin D.

In addition to pharmacological treatments, general measures such as a calcium-rich diet, adequate exposure to the sun and regular physical activity should be encouraged.

Orthogeriatric collaboration and orthogeriatric models

Many practitioners consider that femoral neck fracture is a geriatric rather than an orthopaedic condition. However, these elderly patients often stay for at least a week in orthopaedic departments where the care teams have little awareness of geriatric problems. The National Service Framework for Older People in England recommends that every hospital should have at least one orthogeriatric ward,[1] whose ideal model in terms of efficacy, and also of cost-efficacy, remains to be defined. Orthogeriatric care must be not only a multidisciplinary activity but also a radical alternative to the traditional model, where all strategies that have demonstrated their efficacy in improving the prognosis of proximal femoral fracture are applied. From a review of the literature of the last 10 years, five existing models of collaboration between geriatricians and orthopaedic surgeons may be described:

1 *The traditional model* in which the patient is managed in the orthopaedic department, then transferred to the rehabilitation department and has access to geriatric consultations as required.

2 *A variant of this model*, in which a geriatric team intervenes at admission and at discharge from the orthopaedic department, thus sharing in the management of geriatric problems and in referring patients to the various rehabilitation services.

3 *The integrated model*, where orthopaedists and geriatricians share the management of medical and surgical problems, with the aim of rapid transfer to a geriatric rehabilitation unit.

4 A more *geriatric model*, where the patient is followed preoperatively by a geriatric team and is transferred immediately after surgery to a geriatric unit and then to a rehabilitation facility.

5 Lastly, a *comprehensive orthogeriatric approach* with uninterrupted geriatric management from admission to discharge and daily follow-up of the operated patient by the orthopaedist.

The 2009 update of the Cochrane review by Cameron *et al.*,[47] including two supplementary trials, was not able to demonstrate the superior efficacy of any one of these

models, but emphasized a trend in favour of systems which strengthened genuine links between geriatricians and orthopaedists instead of juxtaposing their interventions. Cost studies are not in favour of this mode of functioning, which, however, should avoid the loss of time related to the various transfers, make it easier for the patient to adjust by doing away with changes of care team and relieve the pressure on the orthopaedic services.

This raises the question of whether it would not be legitimate to change our strategy and develop new models of orthogeriatric care, with early supported discharge or hospital at home and the intervention of a multidisciplinary team to organize rehabilitation.

Key points

- Femoral neck fracture is a 'condition of age' with a severe vital and functional prognosis.
- Current treatment is surgical: internal fixation or hip replacement.
- This condition demands multidisciplinary reflection bringing together the anaesthetist, surgeon, geriatrician and physiatrist.
- Each patient must receive individualized management in order to prevent new fractures.

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CHAPTER 94

Diseases of the joints

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Introduction

The clinical presentation of arthritis is one of joint pain, swelling, morning stiffness and limitation of motion. These are symptoms common to all types of arthritis. Different diseases of the joint can present with signs and symptoms that appear quite similar. There are over 100 types of arthritis that can affect the elderly with osteoarthritis and rheumatoid arthritis being the most common entities. Nevertheless, a thorough medical history and physical examination, together with radiographic and laboratory testing, will identify the correct diagnosis in most cases of diseases of the joints. Arthritis has to be differentiated from periarticular or other musculoskeletal pain syndromes that commonly occur in the aged.

Osteoarthritis

Osteoarthritis (OA) or degenerative joint disease is a chronic disorder characterized by softening and disintegration of articular cartilage with secondary changes in underlying bone, new growth of cartilage and bone (osteophytes) at the joint margins, and capsular fibrosis.[1] It is by far the most common form of chronic arthritis among the elderly. Its prevalence increases with age, occurring in greater than 50% of individuals older than 60.[2] OA is particularly common in elderly people, affecting more than 80% of those older than 75 years.[1] Susceptibility to OA involves systemic factors affecting joint vulnerability including age, gender and genetic susceptibility, nutritional factors, intrinsic joint vulnerabilities including previous damage, muscle weakness and malalignment, and extrinsic factors including obesity and physical activity.[1,3] The most common joints involved are those of weight-bearing including the knees, hips, cervical and lumbosacral spine, proximal (PIP) and distal (DIP) interphalangeal joints of the hands, first carpometacarpal joints (CMC), and metatarsophalangeal joints (MTP).[1] Involvement is typically symmetric, although it can be unilateral at first depending on previous trauma or unusual stress. The pain may be insidious and relieved by rest initially, but as the disease progresses it becomes persistent and more severe with activity. Stiffness following periods of inactivity may also become common. The patient may complain of problems such as knee locking, unsteadiness, or giving away. Some patients, especially women, experience inflammatory OA or erosive OA, which involves particularly the PIPs and DIPs of the hands. These may exhibit inflammatory manifestations such as redness, tenderness and local heat. Knees are often swollen with synovial fluid produced. Cervical and lumbosacral pain is a result of arthritis of hypophyseal joints, bony spur formation, pressure on ligaments or other surrounding tissues, or reactive muscle spasm. Impingement on nerve roots by osteophytes can cause radicular symptoms. Cord compression may result in spinal stenosis. In the cervical area, it causes localized pain and gait unsteadiness. In lumbar areas, it may result in spinal claudication, consisting of pain in the buttocks or legs while walking that is relieved after 10–15 mins of rest. Lumbar flexion and sitting usually relieve these symptoms, as opposed to aggravation of radicular disc symptoms by these positions.[4]

Examination of the joints may detect crepitus, deformities, subluxation, swelling, bony overgrowths such as Heberden's nodes of the DIPs, Bouchard's nodes of the PIPs, or CMC joints, and limitation of motion. Neurological evaluations may detect a radicular pattern of motor or sensory abnormalities, lower motor neuron or upper motor neuron signs in spinal stenosis, and sphincter abnormalities.[5]

No diagnostic laboratory tests are currently available (Table 94.1). The synovial fluid, when present, is noninflammatory with a white count less than 1000 cells/mm^3. Radiological abnormalities may lag behind symptoms. Typical findings are joint space narrowing, subchondral sclerosis, osteophytes and periarticular bone cysts. Oblique films of the spine must be obtained to evaluate the neuroforamina. Computerized tomography (CT) or magnetic

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Table 94.1 Studies to screen for arthritis.

Complete blood count (CBC)
Urinalysis
Erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP)
Chemistry panel including studies for kidney, liver, muscle, and uric acid
Rheumatoid Factor (RF), Anti-cyclic citrullinated peptide antibodies (αCCPAb)
Antinuclear antibody (ANA) and profile if indicated
Synovial fluid analysis if indicated (white count, crystal analysis, cultures)
X-rays of appropriate joints or spinal areas

resonance imaging (MRI) give better evaluation of the spinal pathology and can differentiate OA changes from discopathy, another common problem in older persons.[4]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory symmetrical disease of joints of unknown aetiology, affecting about 1% of the general population worldwide and about 2% of persons 60 years of age and older in the United States.[6,7] Extra-articular manifestations may also contribute to disease symptomatology.[8] Most elderly patients with RA have the disease onset before age 60 and commonly present with additional therapeutic problems when older because of the long duration of the disease and other illnesses. Older persons are more likely to develop joint deformities. Involvement of the cervical spine may result in pain, decreased range of motion and neurological deficits. Extra-articular manifestations, such as rheumatoid nodules, secondary Sjögren's syndrome (SS), and vasculitis are more frequent in this group of patients.[8]

Patients with elderly onset RA (EORA) are those in whom RA develops after age 60. Most patients present with a gradual onset of pain, swelling and stiffness in symmetrical joints, while in others the onset may be more acute. Fatigue, malaise and weight loss may be present. Joint symptoms are characteristically symmetric, although asymmetric presentation may occur. In the aged, asymmetric involvement may be seen in hemiplegic patients with sparing of the paralysed side. All peripheral joints may be involved, but the most common are the PIPs and metacarpophalangeal (MCPs) of the hands involved in 90% as are the wrists, MTPs and ankles. Knees, hips, elbows and shoulders are present to a lesser extent. DIPs of the hands are usually spared. Large joints are commonly involved in EORA, the shoulders more often than in younger patients.[8,9]

The majority of patients experience intermittent periods of active disease alternating with periods of relative or complete remission. A minority will suffer no more than a few months of symptoms followed by complete remission, whereas a small group will have severe, progressive disease. EORA is considered by many to be milder than RA developing at a younger age, which may be related to the lower incidence of rheumatoid factor (RF) positivity in the elderly.[9] RF-positive EORA patients are likely to have more severe disease.[6] Anti-cyclic citrullinated peptide antibodies (αCCPAb) are also found in patients with more severe EORA, but overall to a much lesser extent than younger patients with RA. Most laboratory abnormalities are not specific for RA, with the possible exception of high-titer 19S IgM RF and αCCPAb (Table 94.1). It should be noted that RF in low titers may occur in a small percentage of healthy older individuals, so a positive RF test itself may be not diagnostic. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually increased in RA, often correlating with disease activity. Radiological evaluation of involved joints in early stages is likely to show only soft tissue swelling. Later, the typical findings of symmetric joint space narrowing and erosions can support the clinical diagnosis (Table 94.1).[5,6,8]

Gout

Gout is an inflammatory arthropathy caused by deposition of sodium monourate crystals in the joint and occurs in an overall prevalence from less than 1–15%.[10] Its prevalence increases with age.[10] The typical presentation is that of an acute monoarthritis in 85–90% of first attacks, most commonly occurring in the first MTP joint. The joint is usually extremely tender because it is associated with swelling and overlying erythema that sometimes mimics cellulitis or septic arthritis. Patients may be febrile and attacks can be precipitated by alcohol intake, use of diuretics and stress, such as that occurring with surgical procedures or acute medical illness. Gout occurs more readily in joints damaged by other conditions such as OA. Polyarticular involvement of gout is not uncommon in older persons. It sometimes resembles RA. Such attacks tend to have smouldering onset and longer course with a duration as long as three weeks. Chronic tophaceous gout is characterized by episodes of acute arthritis, chronic polyarthritis, joint deformities and tophi. Radiographic findings are non-specific in early stages. Punched out lesions or periarticular bone with overhanging borders are typically seen in chronic gout.[5,10]

Laboratory findings include hyperuricaemia in most cases.[10] Most individuals with hyperuricaemia never experience acute or chronic gout. About 10% have normal serum levels during the attack. Therefore, the diagnosis should be established by the identification of typical sodium monourate crystals in synovial fluid, preferably with the use of a polarized microscope. This is accompanied by evaluating serum uric acid level and also performing a 24-hour

urine for total serum urate spillage to define if the patient is an over-producer or under-secreter of uric acid.

Calcium pyrophosphate deposition disease

Calcium pyrophosphate deposition disease (CPDD) is also a crystalline deposition arthropathy.[11] Women may be more commonly affected by CPPD crystal deposition than men.[12] Its prevalence increases with age, being 10% in age 60–75 years and 30% in those 80 years of age or older.[13] Most cases are primary, but in some people it is associated with certain conditions such as hypothyroidism, hyperparathyroidism and haemochromatosis. Many patients merely have asymptomatic chondrocalcinosis, commonly noted by X-rays in the knees and wrists where linear punctate radiodensities are found within the cartilage.[11]

Typical presentation is usually of two types, chronic arthropathy, which is sometimes polyarticular and presents with or without acute attacks with the knees most predominantly affected. Clinically, it may resemble OA or RA. Radiography may show features of both OA and CPDD, so it is not clear whether CPDD is primary or secondary. The second presentation is pseudogout, which is an acute monoarthritis, affecting mainly the knees and other large joints primarily and these resolve spontaneously within three weeks. It may infrequently affect a few articulations. Attack of pseudogout can be precipitated by stress or local trauma and fever is common.[12]

Connective tissue disease

Connective tissue disease, primary SS and systemic lupus erythematosus (SLE), may present in the older population. Fifteen percent of cases of SLE may begin after age 55.[14] It may present with arthralgias or symmetric polyarthritis involving primarily finger joints, best resembling RA at this stage. Previous studies indicated older onset SLE tended to be milder than the disease in younger patients with a lower incidence of nephropathy, neuropsychiatric manifestations, fever and Raynaud's symptoms.[15] However, a recent study suggested that older age-onset SLE is not benign.[16] There is an increased frequency of serositis, interstitial lung disease, myalgias and sicca symptoms.[14] Primary SS also often presents in the aged.[17] Patients complain of dryness of their eyes and also dryness in their mouth with swallowing difficulty. Nasal dryness, hoarseness, bronchitis, and skin and vaginal dryness may occur. The parotid glands may be swollen. Sicca symptoms (dry eyes and dry mouth) may be subtle and not obvious to the patients. Individual patients commonly have polyarthritis or arthralgias. Other features of the disease are myalgias, low-grade fever and fatigue. Most have hypergammaglobulinemia and the frequency of developing lymphoproliferative disease is increased.[17]

Antinuclear antibodies are present in most SS and SLE patients, with antibodies to SS-A (Ro) and SS-B (La) occurring in the SS patients and SLE patients; and SLE patients having antibodies alone to double-stranded DNA, Sm and RNP.[18] Other laboratory studies for evaluation include complement levels, antiphospholipid antibody studies, and other specific tests that may be helpful in diagnosing a particular connective tissue disease that is involved in the elderly patient.[19,20]

Drug-induced lupus (DIL) is also a disease of older patients because inciting drugs are prescribed more frequently in the elderly. Symptoms are mild in most patients and resemble those of older onset SLE. The diagnosis is suggested by a history of administration of drugs like procainamide, hydralazine, alpha-methyldopa, propylthiouracil, or minocycline.[21] Most of these patients have positive ANA tests and antibodies to histones or chromatin in 70–95% of the cases and occasionally antibodies to myeloperoxidase. Other antibodies occur infrequently.[22]

Infectious arthritis

Infectious arthritis typically presents as an acute monoarthritis of a large joint in more than 80% of cases with the knee involved in more than 50% of cases.[23] It is associated with systemic signs of infection such as high fever, chills and leukocytosis. Several factors predispose to an infected joint, including pre-existing joint disease, a prosthetic joint, an infectious process elsewhere, or an immunocompromised state, such as diabetes mellitus or treatment with corticosteroids or immunosuppressives.[24] Infectious arthritis has to be entertained in all elderly patients with arthritic complaints. The presentation may be atypical in the aged because normal leukocyte counts and a normal temperature are not uncommon.[24] In all cases of monoarthritis, synovial fluid should be aspirated, a Gram stain and culture performed, and a leukocyte count and differential determined. The leukocytes counts are usually $>50\,000$ cells/mm^3, primarily neutrophils; however, the initial count may be less than $10\,000$ cells/mm^3.[25] The most common pathogen is *Staphylococcus aureus*, followed by streptococci and gram-negative bacilli.[23] *Staphylococcus epidermidis* is common in a prosthetic joint infection. Early diagnosis is mandatory to prevent the high rate of complications; a 19% mortality rate has been reported, and 38% of patients may develop osteomyelitis.[24] Treatment of infectious arthritis is determined by the organism isolated and then appropriate therapy.

Treatment

Effective treatment of elderly arthritic patients combines physical therapy, medications and in some cases, surgical intervention (Table 94.2).

Table 94.2 Treatment modalities for arthritis in the aged.

Physical therapy
Medications
• (Non-inflammatory arthritis)
–Analgesics
–Non-steroidal anti-inflammatories
• (Inflammatory arthritis)
–Non-steroidal anti-inflammatories
–Disease-modifying agents
–Biologics
–Corticosteroids
Surgery

Physical therapy

The value of physical therapy in improving the QOL of the elderly patients with arthritis cannot be overemphasized. The main goals are pain relief, prevention of deformities and maintaining mobility and independence.[5] Pain is relieved by periodic rest, splinting of affected joints and locally applied heat. Although rest decreases joint pain and swelling, it may contribute to the development of contractures, disuse atrophy of muscles and osteoporosis. In the aged, even brief periods of rest can result in loss of muscle strength and difficulty in resuming activities. An individual must maintain a certain level of activity even in the presence of active disease. Initial periods of relative rest should be followed by a programme of passive and then active exercises designed to maintain range of motion and muscle strength. The patients should be encouraged to participate in body toning exercise programmes such as regular swimming, walking, or water aerobics-type programmes. Foot, hand and cervical spine involvement can be helped with proper individualized footwear, paraffin baths and cervical collars, respectively. Fabricated orthoses can help maintain alignment and support mechanically deranged joints. Assistive devices for walking, dressing, eating and bathing can greatly improve the QOL of these patients.[5,26,27]

Medications

Treatment decisions should consider several age-related changes that may affect drug absorption, distribution, metabolism and elimination. The possibility exists that various treatments will have altered efficacy and be potentially more hazardous. Also, many elderly patients with arthritis have other diseases requiring other medications that could cause drug–drug interactions with the arthritis preparations.

Analgesic medications are given for mild arthralgias, especially for OA. Acetaminophen is commonly prescribed at a daily dose of 650 mg three to four times a day as needed. It has been shown to have equal efficacy to other anti-inflammatory agents for pain relief. It is a safe drug when used in therapeutic doses. It appears to be safe for patients with renal dysfunction or peptic ulcers; however, liver function studies must be followed to be sure there are no problems with hepatic toxicity.[28] Other analgesics and opioid receptor agonists are effective in pain management, but their use should be limited to short term, because abuse can lead to adverse effects, such as respiratory depression, drowsiness, constipation and addiction. The recent use of glucosamine and chondroitin sulfate for OA have been investigated and may be efficacious, especially glucosamine in some patients with OA of the hips and knees.[28] Diabetics and patients allergic to shellfish should not use these compounds. Also, the use of intra-articular injections of hyaluronic acid have been helpful to preserve knee cartilage and hip cartilage in some cases.[29,30] Topical agents such as capsaicin and 1% diclofenac gel can also be helpful.[28] Lastly, obesity is also an important risk factor in OA; therefore, regimens of weight loss and exercise can decrease pain and disability, especially of the knees and hips.[28]

Non-steroid anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications for arthritis.[5] In many cases, they are alone sufficient to induce the desired effect. The use of NSAIDs as primary therapy for older patients with OA and RA is not without problems.[27,31] Advanced age has been identified as a primary risk factor for adverse gastrointestinal (GI) events in users of NSAIDs.[32] Hospitalization for bleeding of the stomach or oesophagus occurs far more frequently in older patients who use NSAIDs than those who do not. However, patients are often asymptomatic. The risk factors for such events are advanced age, a history of GI problems, and the simultaneous use of corticosteroids, anticoagulants, alcohol, or tobacco. These factors should be documented in individual patients and treated accordingly.[32] Adverse events such as epigastric pain, mental changes, fluid retention, changes in blood pressure, and occult or gross blood loss should be monitored closely. A complete blood count (CBC), urinalysis, and liver and kidney function tests should be drawn initially for baseline, then in one month, and every three months thereafter to monitor toxicity in the elderly population. NSAIDs such as naproxen, meloxicam, sulindac and diclofenac have proved very effective in the treatment of OA or RA in patients. A concern about peptic ulcer disease has been relieved considerably by the availability of cyclooxygenase-2 (COX-2) inhibitors.[33] However, caution is still needed in older patients who have a history of ulcer disease. Some physicians still add proton pump inhibitors to this therapy when it is used in high-risk patients. Also, the use of H2 blockers such as famotidine, can also be helpful. Both the older NSAIDs and COX-2 selective NSAIDs have the potential for decreasing renal blood flow causing fluid retention, creating abnormal salt and water metabolism,

and interfering with drug excretion, so they are not without their toxicity in the elderly population.[34] The COX-2 antagonists celecoxib and etoricoxib have been used extensively and have other advantages beyond decreased gastric acidity.[35] Clinical trials of these drugs have shown no effect on platelet aggregation or bleeding time at therapeutic doses and do not alter the anticoagulant effect of warfarin. However, the possibility of increased blood pressure, peripheral oedema, or predisposal to myocardial infarctions or strokes because of their effect on thromboxane A2 levels may be a contraindication to using some COX-2 inhibitors in the elderly population.[33]

The nephrotoxic effect of NSAIDs are well documented. The most common mechanism leading to renal dysfunction is inhibition of renal prostaglandin synthesis, which may adversely affect renal blood flow in certain situations, leading to acute insufficiency.[34] At special risk are patients with pre-existing changes in renal function, such as those changes related to ageing, diabetes mellitus, hypertension, congestive heart failure, or use of concomitant diuretics. Preferably, NSAIDs should not be prescribed to patients with these conditions or anybody with a creatinine of 1.5 or higher. NSAID-related psychotic reactions and depression occur more commonly in the aged. Also, NSAIDs can interact with several medications commonly used in older persons, mainly anticoagulants, oral hypoglycaemics, digoxin, seizure medications and lithium.[31] Combining NSAIDs with potassium-sparing diuretics increase the risk of hyperkalaemia.

In RA, the baseline therapy is the use of an NSAID and two remittive agents usually hydroxychloroquine and methotrexate or sulfasalazine to reduce erosions and joint space narrowing which generally occur in the first two years.[6] Hydroxychloroquine in doses of 200 mg once to twice daily is begun. It is considered to be effective in mild-to-moderate cases of RA. It is also effective in treating the arthritis and skin manifestations of SLE and SS and should be prescribed in all of these patients.[36] The third drug in the United States is usually methotrexate in doses of 10–25 mg weekly or in Europe sulfasalazine at doses of 2–3 g daily. These regimens appear to be effective for elderly patients with RA, as it is for younger ones. Methotrexate may have some toxicity in elderly, but is limited mainly to hepatotoxicity and in those with abnormal renal function. The lowest reasonable dose should be used.[32,36] CBC, urinalysis and comprehensive metabolic panel at baseline and in two weeks if changing dosages; otherwise, every six to eight weeks to monitor toxicity are recommended. Also, to reduce toxicity, the use of folic acid at 1–2 mg per day is very helpful. Sulfasalazine at 2–3 g daily should also be monitored at baseline and every two months by a CBC, urinalysis and comprehensive metabolic panel to reduce toxicity. Other remittive agents such as azathioprine at 50 mg bid or leflunomide at 20 mg qd, may be used in RA with efficacy.[37] The recent advent of biologics including etanercept, infliximab, adalimumab, anakinra, golimumab, certolizumab pegol and tocilizumab have been very helpful in bringing into remission elderly patients with RA.[38] These biologics inhibit tumour necrosis factor (TNF), interleukin-1 (IL-1), or IL-6. Etanercept, a TNF receptor antagonist, is given as 25 mg twice a week to 50 mg once a week subcutaneously. It has been shown to be very effective in decreasing sedimentation rate, joint activity, arthralgias, and in reducing erosions and joint space narrowing. The same can also be said for the other new biologics which are monoclonal antibodies directed toward TNF. The fully-humanized antibody, adalimumab, is given at 40 mg subcutaneously every two weeks and the chimeric molecule, infliximab, an intravenous preparation, is given at dosages from 3–10 mg kg^{-1} at baseline, two and six weeks, and then every four to eight weeks thereafter. A newer agent, also fully humanized, golimumab, has a longer half-life and can be given at 50 to 100 mg subcutaneously every 4 weeks with methotrexate. The pegylated TNF antagonist, certolizumab pegol, is given in combination with methotrexate at 400 mg subcutaneously initially and at 2 and 4 weeks, and then 200 mg every other week. Tocilizumab, the IL-6 blocking agent, has recently been approved for RA. It is given with methotrexate at 4 to 8 mg kg^{-1} every 4 weeks. Liver enzymes and lipid levels need to be monitored in patients on Tocilizumab.[38] All have been shown to have long-term efficacy and little toxicity. Injection site reactions may occur and are usually managed with local antihistamine or steroid cremes, or antihistamines. The only other common toxicity noted is the possible development of exacerbating an indolent tuberculosis infection. Therefore, a tuberculosis skin test and chest X-ray should be performed at baseline and yearly. Also, the possibility of aggravating any new infection has to be entertained. Therefore, a dose should be held if a viral or bacterial infection occurs. Caution, also should be maintained in giving a biologic to any patient with an artificial joint. A nidus of infection around the metallic implant could be exacerbated. Also, the long-term effect of blocking TNF is not well understood.[39] They should not be used for any patient with a demyelinating disorder[40] and monitoring for any type of lymphoproliferative processes to develop should they occur.[41] IL-1 blocking therapy, anakinra, can also be used in patients with RA, but may also be used in patients with gout. It is given at 100 mg subcutaneously daily, but a high incidence of injection site reactions may occur.[38] T-cell blocker agents have been developed for use in RA. Abatacept, a human immunoglobulin receptor fusion protein of IgG1 and CTLA4, is the first to be approved. CTLA4Ig binds to CD80 and CD86 on antigen-presenting cells, thereby preventing these molecules from engaging CD28 on T cells. Thus, blocking the T cell from proliferating and producing inflammatory cytokines which can activate other inflammatory cells. Abatacept is given at 10 mg kg^{-1}

intravenously on days 1, 15 and 30 and then monthly, but never over 1000 mg at one infusion. Abatacept is now available weekly as a subcutaneous injection. The safety profile is very good.[42] B-cell agents have also been developed. Rituximab is an ant-CD20 monoclonal antibody that binds the CD20 antigen on pre-B and mature B lymphocytes. Dosages of 1000 mg intravenously at base line and day 15 and the possible retreatment at 6 months can be effective in patients failing other biologic regimens. Side effects including infusion reactions, increased infections and mutifocal leukoencephalopathy developing have been reported.[43]

Corticosteroids can be used in low doses of 5–10 mg of prednisone daily in some elderly seronegative RA patients or in patients with remittive seronegative symmetrical synovitis with pitting oedema (RS3PE).[36] However, higher doses predispose the patient to the multiple side effects of steroids in the elderly including sodium and fluid retention, hypertension, hyperglycaemia, osteoporosis, infections and skin changes.[32,36] With the advent of the new remittive agents and biologics, the use of steroids should be diminished to only those who are unresponsive or cannot afford the other agents. If steroids are used, the use of calcium and vitamin D with that therapy should be included to prevent osteoporosis as much as possible. Intra-articular injections of steroid preparations are commonly employed in RA and OA in conjunction with other treatment modalities, especially when symptoms are limited to one or fewer joints.[36]

The treatment of acute gout in the elderly is still the use of colchicine, but at lower doses than in the past.[32] Generally, the dosage for long-term use of colchicine is one or two 0.6 mg tablets per day depending on the patient's renal function; however, only 0.3 mg in patients aged 70 years or older. When parental colchicine is used, the maximum dose used for an acute episode, in or out of the hospital, should be 1 mg per day intravenously. In renal compromised patients, the use of colchicine has resulted in neuromyopathy.[44] Allopurinol, a xanthine oxidase inhibitor, is another gout medication which can lower serum urate levels. It is best started slowly at 100 mg per day. If the hyperuricaemia is not responding, the dosage should be advanced to 100 mg twice a day and then finally up to 300 mg per day or higher depending on creatinine and uric acid response.[5] Platelet counts and hypersensitivity reactions should be monitored. A new medication, febuxostat, also a selective xanthine oxidase inhibitor in doses of 40–80 mg per day has been shown to be effective in controlling hyperuricaemia and gouty flares.[45,46] Anti-inflammatory agents in acute gout can be used, such as naproxen or the COX-2 inhibitor, etoricoxib.[10] In general, uric acid-lowering therapy should be administered when there are tophi, frequent attacks of gouty arthritis over three per year, or evidence of uric acid overproduction is documented. Baseline 24-hour urine of uric acid spillage over 750 mg per 24 hours or uric acid levels over 6.5 mg dl^{-1} may indicate the need for therapy.[10] Lastly, in refractory gout it has become clear that the inflammasome plays a role in the initiation of acute gout. IL−1β is released. In such patients, IL-1 blockade with anakinra at 100 mg subcutaneously daily till the flare resolves may be effective.[47]

In the treatment for pseudogout in adult patients, it has been shown that colchicine is less effective and is usually being managed by NSAIDs. The dosage of naproxen 500 mg bid, etoricoxib 60 mg once to twice a day, or diclofenac 50 mg tid can be very effective in the long-term management of patients with pseudogout.[13]

Surgery

The major goals of various orthopaedic procedures are to relieve pain and to improve function.[5] Joint replacement, tendon repair, carpal tunnel release and synovectomy are some of the frequently employed measures in RA.[48] In OA, treatments include bunion resection, decompression of spinal roots, and total knee and hip replacements. Arthroscopic lavage of knees has been reported to improve symptoms, but has not been widely employed as a therapeutic measure. Age itself is neither a contraindication to surgery nor a predictor of poor results. Rather, the presence of concurrent medical problems such as heart failure and pulmonary disease contribute more to perioperative morbidity and outcome. The goals, indications and timing of surgery should be individualized depending on the patient's general health status, function impairment, degree of pain and rehabilitation potential.[49]

In summary, arthritis is a common condition among the aged. The most common type is OA and the most common inflammatory process is RA. Optimal management includes physical therapy and medication, possibly combined with surgery, if necessary. Treatment modalities should be offered sometimes to accommodate age-related changes, and body mechanics and function. The long-term medical management of arthritis in the elderly requires close monitoring for potential adverse effects of medications.

Key points

- Arthritis is a common chronic condition among the aged.
- Osteoarthritis is the most common type.
- Rheumatoid arthritis is the most common inflammatory arthritis and can produce long-term morbidity if not treated aggressively.
- There are more than one hundred types of arthritis affecting the elderly.
- Gout, pseudogout, or infectious arthritis can present as red, hot, swollen joints and only synovial fluid aspiration can differentiate.

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SECTION 10

Endocrine and Metabolic Disorders

CHAPTER 95

Endocrinology of ageing

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Introduction

Hormones flow from the ductless glands into the circulation and regulate the metabolism of the body, and with ageing there is a decline in the circulating levels of a number of hormones. Deficiency of some of these hormones produces symptoms and signs similar to the changes seen with ageing. This has led different authorities to suggest that ageing is due to an endocrinopause and that replacement of one or more hormones will result in a reversal of the ageing process. Thus, it has been claimed that the ageing process is due to the somatopause, adrenopause, menopause or andropause. However, hormonal replacement has been as likely to produce negative effects as it has to lead to rejuvenation. Ageing is also associated with changes at the receptor or postreceptor level that can alter hormonal responsiveness.

Hormonal regulation and ageing

Hormones are regulated by a classical negative feedback system. Each peripheral hormone is regulated by a central system consisting of the hypothalamic–pituitary unit. The hypothalamus produces releasing hormones (and occasionally inhibitory hormones) that create a feedforward system that regulates the pulsatility and the circadian rhythm of hormone release. These releasing hormones regulate the release of anterior pituitary hormones, which in return result in the release of endorgan hormones. The endorgan hormones then feed back at the pituitary and the hypothalamic level to inhibit further release of pituitary hormones (Figure 95.1). When disease occurs in the endorgan hormone, it leads to failure of the endorgan and, therefore, negative feedback with an increase in the pituitary hormone (HYPO-disease) or increased activity of the endorgan with suppression of pituitary hormone release (HYPER-disease). When this occurs, the disease is considered to be primary endorgan disease, for example, primary hypothyroidism. Alternatively, failure can occur in the hypothalamic–pituitary unit, leading to a decrease in both the pituitary and the endorgan hormone, and this is known as *secondary disease*, for example, secondary hypogonadism. Finally, excess production of either a hypothalamic releasing hormone or pituitary hormone can occur. An example of this central form of HYPER-disease would be Cushing syndrome.

Ageing has effects on all levels of the hypothalamic–pituitary–gonadal axis. The circadian rhythm is controlled by the suprachiasmatic nucleus, which feeds information to the hypothalamus. The hypothalamic releasing hormones are responsible for maintaining the pulsatility of hormone release, which is essential for optimal hormonal action. With ageing, the pulse generator leads not only to a decline in maximal hormone production, but also to an irregular or 'chaotic' production of hypothalamic releasing hormones. This is amplified at the pituitary level where there is a decrease in the ability to respond to the hypothalamic signal. In addition, the endorgan itself has decreased responsiveness to the stimulus from the pituitary hormone[1-4] (Figure 95.2).

In addition, changes in hormonal binding to its receptor and postreceptor responsiveness can also occur with ageing. An example is the posterior pituitary hormone, arginine vasopressin (AVP) or antidiuretic hormone (ADH). There is a decline in the renal responsiveness to AVP with ageing, which leads to an increase in basal secretion of AVP. A small further increase in AVP then puts the older person at high risk of developing hyponatraemia and syndrome of inappropriate ADH.[5] There is also an attenuation of the normal increase in AVP that occurs at night. This increase is important for reabsorption of fluid during sleep and, therefore, its attenuation with ageing leads to increasing nocturia.[6]

Classically, endocrinologists have interpreted circulating hormone levels in the absence of an understanding of the functioning of the receptor. This is becoming less acceptable, as was shown recently by the example of the

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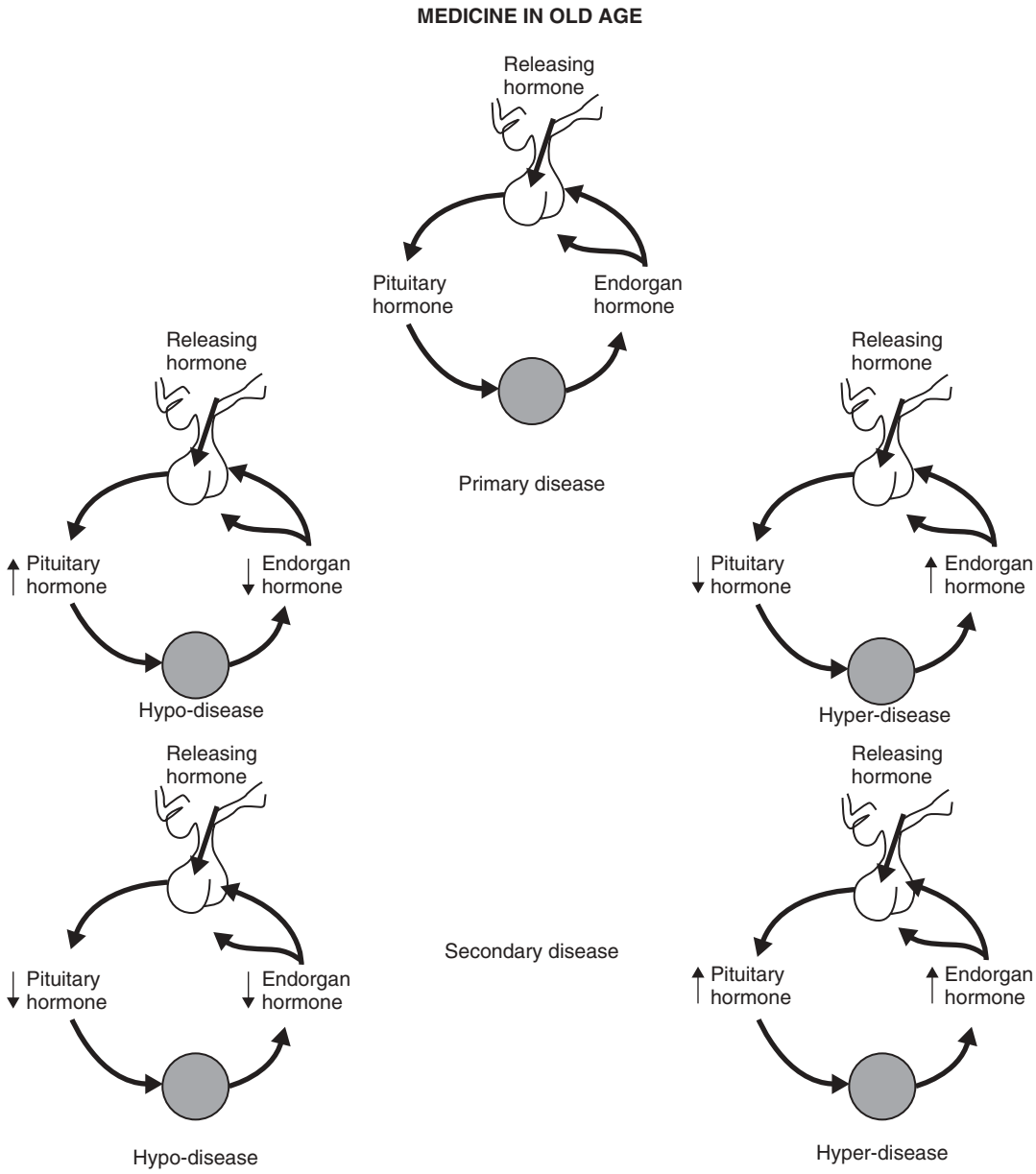

Figure 95.1 The normal hypothalamic–pituitary–endorgan and the effects of disease processes on it.

testosterone receptor and prostate cancer. The testosterone receptor contains a number of CAG repeats. The more the repeats, the less responsive the receptor is to testosterone. Prostate cancer occurs less often in males with a higher number of CAG repeats.[7]

Table 95.1 lists the hormonal changes seen with ageing. The levels of circulating hormones are determined by their production and clearance rates. Thus, the level of thyroxine remains normal because both the production and clearance rates decrease equally. Cortisol levels are slightly increased as there is a greater decrease in clearance rates. Cholecystokinin levels increase markedly due to the decline in clearance rate.[8]

It is generally believed that free hormone or tissue-available hormone levels determine the effectiveness of the hormone. Thus, in the case of testosterone in males, there is a marked increase in sex hormone binding globulin (SHBG) with ageing. The testosterone bound to SHBG is thought not to be available to tissues (Figure 95.3). The rest of the testosterone is free or bound to albumin, which is thought to be tissue available. Hence measurement of the bioavailable testosterone gives a more accurate reflection

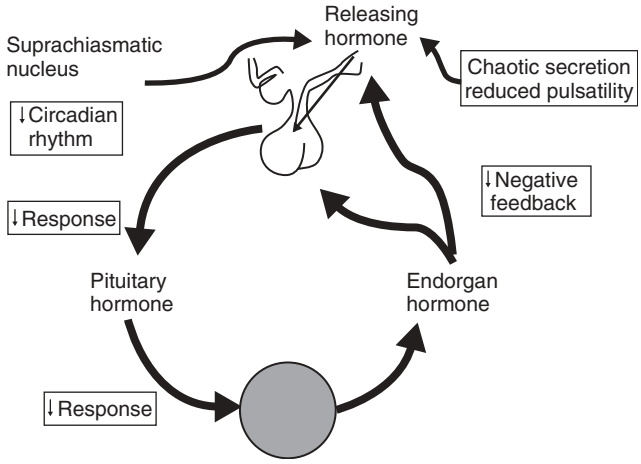

Figure 95.2 Effects of ageing on the hypothalamic–pituitary–endorgan axis.

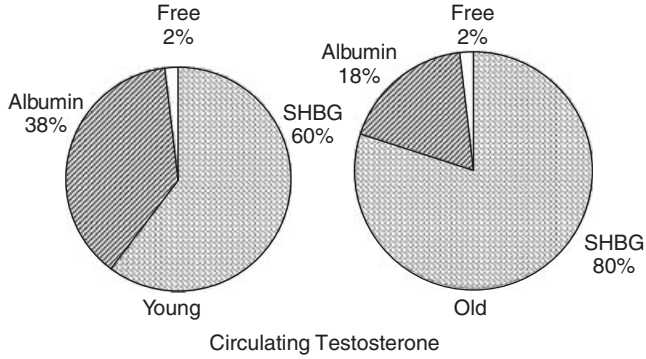

Figure 95.3 Effect of altered binding proteins with ageing on the effect of tissue-available hormones: the example of testosterone.

of the true testosterone level than does a total testosterone measurement.[9] Similarly, a number of growth hormone-binding proteins can produce marked changes in the ability of growth hormone to access its receptor.

Effects of ageing and related diseases on endocrine diseases

With ageing, there is a blurring of the boundaries between health and disease. The age-related decline in many hormone levels results in difficulties in making the biochemical diagnoses of endocrine disorders. The decreased functional reserve of endocrine organs that occurs with ageing increases the propensity for older persons to develop endocrine deficiency disorders. With ageing there is a decrease in T-suppressor lymphocytes and an increase in autoantibodies. Many endocrine disorders are due to autoimmune disease and these changes amplify the possibility of an older person developing hypoendocrine disease in old age. There is also an increased likelihood of the development of polyglandular failure syndromes.

The decline in receptor and postreceptor responsiveness that occurs with ageing often leads to atypical presentations. Apathetic thyrotoxicosis is due, in part, to the decreased postreceptor responsiveness for β-adrenergic receptors that occurs with ageing. The classical changes of apathetic thyrotoxicosis include depression, weight loss, atrial fibrillation, heart failure, blepharatosis and proximal myopathy. Apathetic thyrotoxicosis occurs only in about 7% of older persons with hyperthyroidism. The presentations of endocrine disease in older persons are further confused by the fact that they often present with non-specific symptoms, for example, delirium, fatigue, falls, weight loss, cognitive decline or depression. These symptoms are common in older persons and can lead to delayed diagnosis. For example, Addison's disease can present with weight loss, fatigue, abdominal pain, diarrhoea and hyponatraemia. The increase in cancer with ageing can lead to ectopic hormone production with an increase in endocrine disorders such as the syndrome of inappropriate ADH.

Table 95.1 Hormonal changes associated with ageing.

Decreased	Normal	Increased
Growth hormone	Estrogen (men)	ACTH
Insulin growth factor-1	Luteinizing hormone (men)	Cholecystokinin
Testosterone	Thyroxine	Insulin
Estrogen (women)	Pancreatic polypeptide	Amylin
Dehydroepiandrosterone	Gastric inhibitory peptide	Luteinizing hormone (women)
Pregnenolone	TSH	FSH
Triiodothyronine	Glucagon-releasing peptide	Vasoactive intestinal peptide
25-(OH)-vitamin D	Epinephrine	Cortisol
$1,25\text{-}(OH)_2$-vitamin D	Prolactin	Parathyroid hormone
Aldosterone		Norepinephrine
Calcitonin		Glucagon

Polypharmacy is common among older persons. This can lead to (1) interference with hormonal and metabolic measurements, for example, vitamin C interferes with the measurement of glucose; (2) altered circulating hormone levels, for example, phenytoin and thyroxine; (3) decreased hormonal responsiveness, for example, spironolactone and aldosterone; (4) altered requirement for appropriate hormonal replacement dose, for example, rifampin increases the thyroxine replacement dose; (5) precipitation of latent disease, for example, thyrotoxicosis by iodine-containing medicines; (6) drug–hormone interaction, for example, coumadin and oral hypoglycaemics to produce hypoglycaemia; (7) production of metabolic abnormalities, for example, vitamin A in megadoses produces hypercalcaemia; (8) poor compliance with endocrine replacement therapies; and (9) adverse drug reactions.

Hypothyroidism represents a classical example of an endocrine condition that has major overlap with symptoms commonly seen in older persons. These include cold intolerance, slowed pulse, constipation, fatigue, cognitive changes, erectile dysfunction, dry skin, dry, brittle hair and high blood pressure.

There are a number of endocrine disorders that occur virtually exclusively in older persons. These include osteoporosis, andropause, Paget's disease and endothelin-induced hypertension.

Insulin resistance syndrome and ageing

There is increasing awareness that insulin resistance syndrome is a cause of an accelerated ageing process.[10] This condition is produced by a genetic propensity interacting with overeating and lack of exercise, that is, the couch potato syndrome (Figure 95.4). It is classically associated with visceral obesity, that is, an increase in intra-abdominal fat. This leads to an increased production of tumour necrosis factor α and leptin and a decrease in adiponectin (a hormone that decreases insulin resistance). The insulin resistance syndrome consists of hyperinsulinaemia, diabetes mellitus, hypertension, hyperuricaemia, hypertriglyceridaemia, hypercholesterolaemia, increased small, dense low-density lipoprotein (LDL) molecules, alterations in coagulation status, myosteatosis (fat infiltration into muscle), cognitive decline and non-alcoholic steatohepatitis. Hypertriglyceridaemia is a key in the development of the myosteatosis and the cognitive decline. Persons with insulin resistance have an increased incidence of myocardial infarction and stroke. The insulin resistance syndrome is associated with frailty, disability and increased mortality.

Recent studies have suggested that a major component of the pathogenesis of the insulin resistance syndrome is accumulation of triglycerides and free fatty acids within muscle cells. This can occur either because of a failure of mitochondria leading to decreased utilization of intracellular fatty acids (primary syndrome) or because of excess circulating triglycerides and fatty acids (secondary syndrome). Accumulation of fatty acids within the cell leads to decreased activity of the insulin receptor substrate and, therefore, a decrease in GLUT-transporter activity.[13]

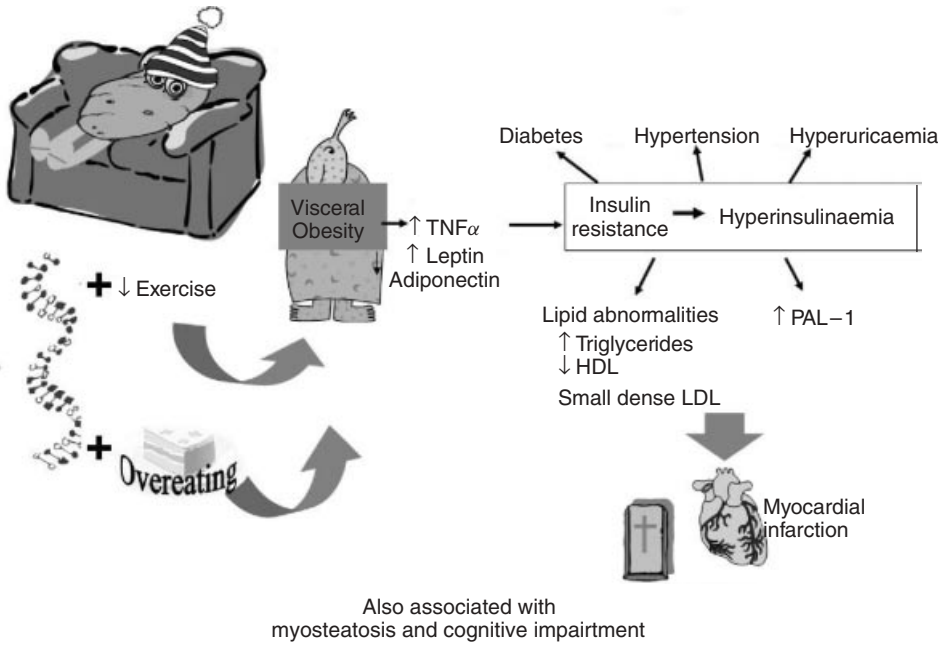

Figure 95.4 Metabolic syndrome: the deadly quintet.[11,12]

The hormonal fountain of youth

The parallel decline of many hormones with ageing and age-related symptoms has led to the suggestion that the hormonal decline may be a central component in the pathogenesis of ageing.[14] Unfortunately, with the exception of the role of vitamin D in age-related loss of bone mineral density, there is little evidence to support this premise. In this section, each of the hormones that have been suggested to play a role in the ageing process will be briefly discussed.

Vitamin D

Vitamin D has been shown in a longitudinal study to decline with ageing.[15] There is clear evidence that vitamin D (800 IU) together with calcium decreases the rate of hip fracture in older persons.[16] This is associated with a decline in mortality. Vitamin D replacement in persons who have clear vitamin D deficiency improves muscle strength and decreases falls.[17,18] Vitamin D deficiency is associated with increased mortality. Vitamin D deficiency should be suspected in any older person with a borderline low calcium level and an elevated alkaline phosphatase. Increased exposure to sunlight may be as efficacious as vitamin D replacement in increasing vitamin D levels. However, there is some evidence that old skin when exposed to ultraviolet light is less effective than young skin at manufacturing cholecalciferol. Ideally, vitamin D levels should be 30 ng dl^{-1} or greater.

Testosterone

Testosterone levels decline in both males and females with ageing. The effects of testosterone replacement in males and females with ageing is shown in Table 95.2. Testosterone replacement at relatively high doses in older males has been shown to increase muscle mass, strength, functional status and bone mineral density.[4,19] Testosterone increases libido in both males and females. In males, testosterone increases erectile strength, volume of ejaculation and visuospatial cognition. The major side effect is an excessive increase in haematocrit. The effects of long-term testosterone replacement on benign prostate hypertrophy and prostate cancer are unclear at present. Testosterone can cause gynaecomastia, produce water retention and may worsen sleep apnoea in a few individuals. The lack of long-term safety data for testosterone is a major concern. At present, testosterone should be considered a quality of life drug in both men and perhaps women (see Chapter 9, Sexuality and ageing; Chapters 99 and 100, Ovarian and testicular function). The development of selective androgen receptor modulators (SARMs) is under way in an attempt to avoid some of the potential side effects of testosterone. Nandrolone has been shown to be a potent anabolic agent in older persons.

Table 95.2 Effects of testosterone in older males and in postmenopausal females.

Older males	Postmenopausal females
Increased muscle mass	Increased muscle mass
Increased strength	Increased bone mineral density
Increased function	Increased libido
Increased bone mineral density	Decreased mastalgia
Increased haematocrit	
Increased visuospatial cognition	
Increased libido	
Increased strength of erection	
Increased volume of ejaculation	

Table 95.3 Lessons from growth hormone studies in older persons.

Growth hormone increases nitrogen retention
Growth hormone produces weight gain
Growth hormone increases muscle mass
Growth hormone possibly increases type-II muscle fibres
Growth hormone does not increase strength
Growth hormone is associated with multiple side effects
Growth hormone may improve function in malnourished older persons

Growth hormone

The concept that growth hormone may be able to rejuvenate older men was given impetus by a publication by Rudman *et al*.[20] in the *New England Journal of Medicine*. Unfortunately, since this original publication, numerous studies have failed to demonstrate any major positive effects of growth hormone (Table 95.3).[21] In addition, growth hormone has been shown to have a variety of side effects when administered for more than 3 months to older persons. There is some evidence that growth hormone may improve weight gain and function in malnourished older persons.[22,23]

Studies in animals have suggested that growth hormone-deficient animals live longer than growth hormone-sufficient animals.[24] Administration of a growth hormone-releasing hormone antagonist increased lifespan in older animals. In addition, in a human study, persons with the highest levels of growth hormone had the highest mortality rate. At present, there is no evidence to support the use of growth hormone to slow ageing or improve the quality of life of older persons.

Insulin growth factor-1 (IGF-1)

Insulin growth factor-1 (IGF-1) is produced in peripheral tissues in response to growth hormone. In human studies, it has tended to produce hypoglycaemia and minimal positive effects. In animals, it accelerates the growth of tumour cells.

Table 95.4 Ghrelin and ageing.

Ghrelin is produced in the fundus of the stomach
Ghrelin is slightly decreased with ageing
Ghrelin increases food intake
Ghrelin releases growth hormone from pituitary
Ghrelin increases body mass
Ghrelin enhances memory
Ghrelin produces its food and growth hormone effects through nitric oxide synthase stimulation
MK-771 (a ghrelin agonist) had minimal effects in older humans

In muscle, three different forms of IGF are produced, one of which is mechanogrowth factor (MGF). MGF levels increase in response to resistance exercise. Stem cell replacement of MGF has reversed the muscle atrophy seen in older rats.

Ghrelin

Ghrelin is produced in the fundus of the stomach and released into the circulation. It causes the release of growth hormone and increases food intake (Table 95.4). MK-771, a ghrelin analogue, while increasing growth hormone, has failed to produce major positive effects in older humans. Some studies have suggested that ghrelin agonists may be effective in frail older persons.

Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) is an adrenal hormone whose levels decline markedly with ageing. It has been touted as the 'mother hormone' by anti-ageing charlatans. DHEA has remarkable effects on the immune system and cognition in rodents. Unfortunately, a year-long study of 50 mg showed no effects on muscle mass or strength and only a small increase in libido in women over 70 years of age and some positive effects on the skin.[25–27] It may have some small effects on insulin resistance. At doses of 100 mg, it has been reported to have effects on humans, but at this dose it is converted into substantial amounts of circulating testosterone.

Pregnenolone

Pregnenolone is produced by the adrenals from cholesterol. It is the true 'mother hormone' as it is the precursor of DHEA. In mice, it is the most potent memory enhancer yet to be discovered.[28] Unfortunately, it has not been shown to have positive effects in humans.

Estrogen

Estrogens were originally touted as hormones that would make women 'feminine forever'. The Women's Health Initiative (WHI) has shown that premarin in older postmenopausal women increases breast cancer, pulmonary embolism, heart disease and Alzheimer's disease while decreasing hip fracture and colon cancer.[29–31] Although there are still scientists pursuing a better (safer) estrogen which will have the positive effects in women without the negative effects, estrogens should be avoided in women over the age of 60 years at present. The use at the time of the menopause represents a quality of life decision. Women with premature menopause should be given hormone replacement therapy.

Melatonin

Melatonin is synthesized from tryptophan in the pineal gland. Melatonin levels increase at night and fall to very low levels during the day. Melatonin has been used with minor success to enhance sleep in older persons. It does not alter the normal sleep structure. It may have a role in the treatment of seasonal affective disorder. Extravagant claims for the utility of melatonin have been based primarily on animal studies and include life extension, enhanced immune function and decreased tumour growth. Studies in humans to support these claims are virtually non-existent. The rate of decline of melatonin with age is less than was originally thought.

Key points

- It has been suggested that multiple hormonal changes occur with ageing which may play a role in the pathophysiological process associated with ageing.
- Many hormones decline with ageing but their replacement does not necessarily reverse ageing effects.
- The role of melatonin and dehydroepiandrosterone in ageing is unknown.
- The insulin resistance syndrome can be considered a cause of the accelerated ageing process.
- Testosterone and other hormones may play a role in the treatment of sarcopenia, which is an important proximate occurrence in the development of functional decline in older persons.

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CHAPTER 96

Water and electrolyte balances in ageing

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Introduction

Water and volume homeostasis are under meticulous control through a complex interrelationship of the hypothalamus–posterior pituitary and the renin–angiotensin–adrenal axis.[1] The elderly, however, are at increased risk for both syndromes of hyponatraemia and hypernatraemia and these disorders are associated with further clinical complications.[2–4] It is therefore important to understand the physiology involved in normal water homeostasis, the potential problems associated with ageing and the possible therapeutic modalities to correct these disorders.

Normal physiology

There is dual control of water and serum osmolality.[1] The hypothalamus and posterior pituitary are involved in water retention and the renin–angiotensin–aldosterone axis is involved in sodium retention.

The supraoptic and paraventricular nuclei of the hypothalamus respond primarily to increases in serum osmolality with the release of vasopressin [antidiuretic hormone (ADH)] Figure 96.1a. The release of ADH is mediated through changes in an electrochemical gradient in these magnocellular neurons to maintain serum osmolality at $285 \pm 2\,\mathrm{mOsm\,kg^{-1}}$. These neurons are also under the influence of neurotransmitters, such as acetylcholine (i.e. through the vagus nerve, as described below), catecholamines, opioids and angiotensin. Small changes in osmolality allow for acute adjustment of serum ADH levels with resulting water retention or free water clearance in the kidney.[1]

There is also a parallel autonomic nervous system regulation of water retention in which vascular receptors respond to decreases in total body water and changes in organ perfusion. There are high-pressure (blood pressure) baroreceptors in the carotid sinus and aortic arch and low-pressure stretch receptors in the cardiac atria and pulmonary venous systems. Both types of receptors transmit regulatory impulses via the vagus nerve to the hypothalamic neurons to stimulate ADH in the event of low effective arterial blood volume (EABV).[1] Pathophysiological states of diminished EABV will stimulate the release of ADH above that due to osmolality. Thus ADH may be 'appropriate' for the diminished EABV, but appears inappropriate for serum osmolality. Conditions which may increase ADH release are shown in Figure 96.1b. The baroreceptors may respond to changes in blood pressure associated with volume loss (gastrointestinal losses or diuretic-induced volume loss), decreased intravascular volume in hypoalbuminaemic oedema-forming states (ascites or nephrotic syndrome), orthostatic hypotension (due to adrenal cortical insufficiency, mineralocorticoid insufficiency or autonomic neuropathy) and decreased arterial perfusion (due to reduced cardiac output such as cardiac tamponade, cardiomyopathy or severe hypothyroidism). Decreased stretch of the volume receptors in the cardiac left atrium may occur in states of low EABV as described above. Diminished stretch in these receptors may also 'appear' as low pressure due to restrictions in pulmonary vascular return to the heart, as a result of increased intra-thoracic pulmonary pressure in severe reactive airway disease or with mechanical ventilation.[1]

Vasopressin activates V2 receptors in the distal collecting tubule of the kidney (Figure 96.2). In the absence of ADH, the tubule is impermeable to water transport. As shown in Figure 96.2, 15–30 l per day of free water may reach the distal collecting tubule. The entire volume may potentially be lost through the urine in central diabetes insipidus (lack of renal concentration ability due to either partial or complete ADH deficiency). In the presence of ADH, water is transported from the intraluminal collecting duct through aquaphorin-2 channels, across a concentration gradient to the intra-renal capillaries to reabsorb free water. The concentration gradient is derived at the loop of Henle through the medullary urea countercurrent system. The urea is freely permeable into the collecting duct. In the presence

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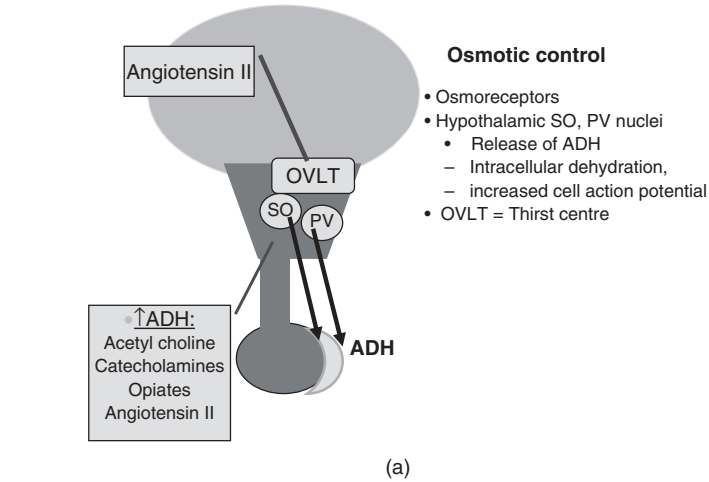

Figure 96.1 (a) Osmotic control of water balance. The hypothalamus supraoptic (SO) and paraventricular (PV) nuclei release antidiuretic hormone (ADH) through neural tracts to the posterior pituitary. Thirst is under control of a closely located series of hypothalamic neurons in the organum vasculosum of the lamina terminalis (OVLT). (b) Pressure–volume control of water and sodium balance. Baroreceptors (systemic blood pressure) in the aortic arch and volume receptors in the atria respond to changes in effective arterial blood volume (EABV) to induce release of ADH through vagal stimuli. Decreased intrarenal perfusion induces renin activation of the renin–angiotensin-aldosterone system to increase sodium retention.

of ADH, the kidney may concentrate the urine to a volume of 0.7 l per day with an osmolality of 600–1200 mOsm kg^{-1}, made up primarily of the secreted urea.

Thirst, the conscious desire to drink, is another active component of water retention.[1,5] Thirst is under control of a closely located series of hypothalamic neurons in the organum vasculosum of the lamina terminalis (OVLT). This area is independent of the blood–brain barrier. These neurons, like the ADH-secreting neurons, are under a similar influence of serum osmolality, neurotransmitters and angiotensin. Normally thirst lags ADH release in response to increases in serum osmolality. The threshold of thirst, as measured on a visual analogue scale or the volume of water ingested, is ~10 mOsm kg^{-1} greater than the ADH threshold.[5] There are pathological conditions in which thirst may be independent of ADH release. Thirst is inappropriately diminished in response to serum osmolality in central nervous system conditions characterized by a reset or diminished thirst response to serum osmolality (essential hypernatraemia) or in complete lack of thirst response to severe hypernatraemia (adipsia) (Figure 96.3).[5]

Whereas ADH is the main hormone involved in water homeostasis, the renin–angiotensin–aldosterone system is the main factor in sodium retention and systemic blood pressure/volume control. Renin is released from the juxtaglomerular apparatus of the kidney in response to low perfusion, low intravascular volume and low tubular sodium. Renin is an enzyme which converts liver-derived angiotensinogen to angiotensin 1 and lung-derived angiotensin-converting enzyme further metabolizes conversion

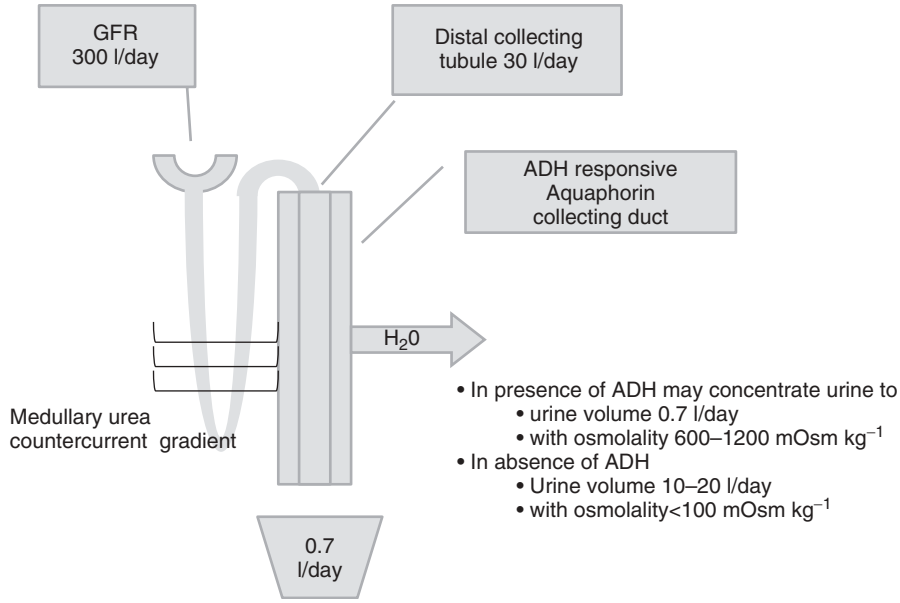

Figure 96.2 Renal action of ADH in water conservation.

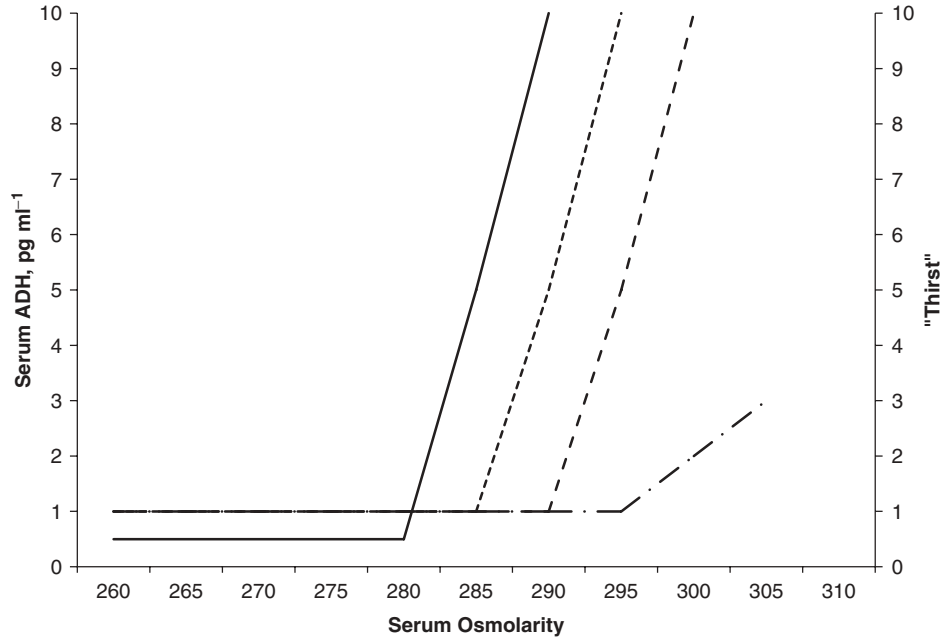

Figure 96.3 Comparisons of disorders of thirst. Serum ADH increases with serum osmolality at a threshold of 280 mOsm kg^{-1} (solid line). Thirst responses increase at approximately 5–10 mOsm kg^{-1} higher than that of ADH release (dotted line). Abnormally decreased thirst responses are found in essential hypernatreamia (dashed line) and severely impeded thirst responses are found in adipsia (dashed-dotted line).

to angiotensin 2. Angiotensin 2 both stimulates the release of the mineralocorticoid aldosterone to retain sodium and stimulates the hypothalamic neurons to release ADH and provoke thirst (Figure 96.1b).

Syndromes of hyponatraemia may reflect physiological 'appropriate' release of ADH in response to vagal stimuli due to decreased perfusion pressure or decreased plasma volume (decreased EABV). In these situations, the elevated ADH is inappropriate for the serum osmolality. The syndrome of inappropriate ADH secretion (SIADH) is a research definition which eliminates appropriate physiological ADH responses. The discussion of hyponatraemia includes both 'appropriate' and SIADH syndromes.

Hyponatraemia may be defined as a serum sodium level $<135\,\text{mequiv}\,l^{-1}$ and for clinically significant hyponatraemia $<130\,\text{mequiv}\,l^{-1}$.[1] Aside from water intoxication associated with excessive water intake during exercise, most causes of hyponatraemia are associated with imbalances in ADH levels.[2–4,6] Clinical syndromes of hyponatraemia (and true hypo-osmolality) are associated with decreased effective serum osmolality,[7,8] where

$$\text{serum osmolarity} = (2 \times [\text{Na}], \text{mequiv}\,l^{-1}) + \frac{[\text{glucose}], \text{mg}\,dl^{-1}}{18} + \frac{[\text{BUN}], \text{mg}\,dl^{-1}}{2.8}$$

Serum concentrations of urea, which are included in the calculation of plasma osmolality, are not considered as part of the calculation of effective extracellular osmolality, since urea is freely permeable through cell membranes.

$$\text{effective serum osmolarity} = (2 \times [\text{Na}]) + \frac{[\text{glucose}]}{18}$$

Therefore, the major component of extracellular osmolality in the non-hyperglycaemic state is serum sodium with its corresponding anions. Severe clinically significant hyponatraemia is usually associated with serum sodium in the range $<120\,\text{mequiv}\,l^{-1}$ or with the rapid decline of serum sodium as in water intoxication or post-anaesthesiology hyponatraemia.[1,6] The major toxicities are due to changes in neurological functions (defined as hyponatraemic encephalopathy).[1,6] Symptoms may range from headache, nausea, disorientation and confusion to more severe symptoms of cerebral oedema with seizures, coma and, in extreme cases, cerebral tentorial herniation and death. Chronic hyponatraemia (which has developed over a time course of >48 h) usually results in central nervous system intracellular adaptation, with the extrusion of intra-neuronal organic and inorganic osmoles. During the treatment of symptomatic hyponatraemia, the concern therefore is that overly rapid correction of hyponatraemia (defined as an increase of $>12\,\text{mequiv}\,l^{-1}$ over 24 h or $>18\,\text{mequiv}\,l^{-1}$ over 48 h) may result in cerebral dehydration and pontine and extrapontine osmotic demyelination syndromes (ODS). These ODS may be delayed in onset and associated with severe neurological morbidity and mortality.[1,6]

Water homeostasis in the elderly

The elderly are prone to disorders of both hyper- and hyponatraemia.[1-6] These abnormalities may be due to the normal physiological changes in the ageing process, intercurrent illnesses or side effects of medications. Normal physiological changes due to ageing may result in a tendency towards hypernatraemia (sodium $>145\,\text{mequiv}\,l^{-1}$).[4,5,9] Although renal function declines with age, fluid homeostasis is not affected by this decline until glomerular filtration rates are as low as $30–50\,\text{ml}\,\text{min}^{-1}$.[4] Compared with younger individuals subjected to water deprivation, healthy older adults have decreased thirst responses and increased serum ADH levels, but decreased urinary concentration and ability to excrete free water.[10,11] The decreased responsiveness of aquaporin-2 to ADH may be due to a physiological decreased aquaporin-2 receptor expression associated with ageing.[12] Also, after age 75 years there is a decrease in total body water from 60 to 50%, potentiating the risk for dehydration over short periods of time.[4]

The institutionalized elderly may be more prone to hypernatraemia.[9,13] Whereas normal elderly patients subjected to fluid restriction may have a decrease in thirst response compared with younger subjects, they retain their ability to secrete ADH. Those with Alzheimer's disease may be more severely compromised by having a more pronounced decrease in both thirst and ADH responses compared with even age-matched controls.[14] In patients with Alzheimer's disease, these thirst responses may fall in the range compatible with essential hypernatraemia[5] and the ADH levels may be inappropriately low for the degree of dehydration and comparable to levels found in states of partial central diabetes insipidus.[14] Unless patients are monitored, elderly institutionalized individuals dependent on caregivers for fluid intake (due to previous stroke or degenerative brain diseases) may not receive adequate fluids at or between meals.[13] These groups of people may have an 18% incidence of hypernatraemia.[5] The incidence of hypernatraemia may be exacerbated during acute intercurrent febrile upper respiratory illness to levels as high as 63%.[9] They may also have concurrent illnesses (such as hypercalcaemia or hypokalaemia) or be prescribed medications (such as lithium), all of which are associated with nephrogenic diabetes insipidus (renal insensitivity to ADH action) and inability to retain water.

Hyponatraemia is also very common in the elderly, as outpatients, inpatients and those in long-term care.[15,16] The prevalence of hyponatraemia among elderly outpatients is 7–11%[4] and for those in long-term care 11–53%.[2,3,15] The causes of hyponatraemia are less clearly defined than for hypernatraemia. There are physiological changes in the kidneys with ageing resulting in a decreased ability to concentrate urine and to excrete free water.[11,17] However, the onset of hyponatraemia may be associated with medication or responses to concomitant illnesses.[15,16] Many medications involved in central nervous system modulation and opioid transmission are associated with ADH secretion. Common agents associated with hyponatraemia in all people include antidepressants (both tri- and tetracyclics), antipsychotic drugs (phenothiazines, butyrophenones), antiepileptic drugs (carbamazepine, oxcarbazepine, sodium valproate) and opioids.[18] The elderly appear to be more sensitive to the hyponatraemic

effects of selective serotonin reuptake inhibitors (SSRIs).[19] Diuretics, owing to their frequent use, are probably the most common medication associated with hyponatraemia, with a prevalence as high as 11% in the geriatric population.[18] Less commonly, other antihypertensive agents such as angiotensin-converting enzyme inhibitors and calcium channel antagonists produce a decrease in effective arterial blood volume (EABV) with physiologically 'appropriate' increases in ADH.[18] True SIADH syndromes, due to ectopic ADH production by cancer or inappropriate ADH due to neurological lesions, are less likely to be the cause of hyponatraemia unless there are positive clinical features. Among 50 elderly hospitalized patients with mild to moderate hyponatraemia, an exhaustive evaluation did not reveal these causes of inappropriate ADH syndrome. The investigators found that the hyponatraemia was associated with pneumonia and medication, although 60% remained idiopathic.[16]

Many patients may have primary orthostatic hypotension, for example, due to autonomic neuropathy in Parkinson's disease and multiple system atrophy or associated with low renin–low aldosterone mineralocorticoid deficiency. Older patients may have excessive treatment of their hypertension. The elderly should be monitored for orthostatic blood pressure changes and have more moderate adjustment of systolic hypertension than younger individuals.[20]

Other medications, not specifically used in the elderly, are associated with hyponatraemia. Antineoplastic agents include vincristine and cyclophosphamide. Vincristine may cause a hypothalamic neuropathy and cyclophosphamide treatment may potentiate an ADH effect at the renal tubule and requires patients to drink large volumes of water to prevent cystitis.[18] Uncommon causes of hyponatraemia associated with common drugs include non-steroidal anti-inflammatory drugs (NSAIDs), which may lower the levels of prostaglandins. Prostaglandins have an anti-ADH effect on the renal tubules, so lowered levels result in potentiated ADH action. Trimethoprim sulfamethoxazole may act as a mild diuretic and cause hyponatraemia if given in high doses or when given to a patient with renal impairment.[18]

Hyponatraemia is associated with a poor overall prognosis.[21] In a retrospective analysis of outpatient community subjects, there was a higher risk of death from cardiovascular disease associated with hyponatraemia.[21] It is not clear whether the hyponatraemia was causative of the increased mortality or whether the hyponatraemia was a comorbidity associated with an underlying congestive heart failure. Similarly, hyponatraemia was associated with gait disturbances, falls and bone fractures.[2,22] In a retrospective study of patients with bone fracture admitted after incidental falls, hyponatraemia was found in 13% of cases versus 4% of controls, $p < 0.0001$.[23] However, this study does not resolve the issue of assigning causality of the hyponatraemia with adverse events. Many of the patients with falls and hyponatraemia had higher incidences of underlying reasons for falls compared with controls. Those with hyponatraemia also were more frequently taking SSRIs (21% vs 15%, $p = 0.006$), benzodiazepines (39% vs 31%, $p = 0.007$) or other CNS class drugs (59% vs 49%, $p = 0.0004$), and had cognitive impairment (17% vs 7%, $p < 0.0001$) or orthostatic hypotension (6% vs 2%, $p = 0.003$). The simultaneous use of medications associated with neurocognitive impairment and hyponatraemia may explain the association of concurrence of hyponatraemia with the high rate of falls.

Therefore, it is important to assess the role of hyponatraemia within the context of a cause and effect relationship and to determine if the neurocognitive symptoms are reversible with correction of the hyponatraemia independent of correction of the underlying illness or of removal of potentially causative medications. Renneboog *et al*.[24] performed a retrospective analysis of patients admitted to an acute care hospital with serum sodium levels between 115 and 132 mequiv l^{-1}. Subjects were excluded from the analysis if they had heart failure, cirrhosis, nephrotic syndrome, acute polydipsic hyponatraemia or seizures and were compared with age- and sex-matched controls. In those with hyponatraemia there was a 21% incidence of falls compared with 5% in the controls ($p < 0.001$). The researchers then prospectively assessed eight subjects with hyponatraemia by tests for abnormalities in gait and cognition. The tests were compared prospectively when they had hyponatraemia (serum sodium 128 ± 3 mequiv l^{-1}) and after correction of hyponatraemia (138 ± 2 mequiv l^{-1}). There were significant improvements after correction of hyponatraemia in abnormalities in gait (as determined through a standardized test of distance travelled by tandem gait on a pressure-sensitive calibrated platform). Direct linear gait improved (measured as a decrease in the total distance covered including erratic gait) from 1336 ± 320 mm vs 1047 ± 172 mm, $p = 0.003$. There were improvements in cognitive tests. determined by a decrease in reaction time on attention tests (from 673 ± 182 ms vs. 615 ± 184 ms, $p < 0.001$). Whether these improvements in neurocognitive functions were due to the correction of the hyponatraemia itself, the correction of the underlying illness or removal of the offending medication causing the hyponatraemia, was not determined.

It was therefore hoped that the issue of causation of mental status changes with hyponatraemia would be resolved by the correction of the hyponatraemia independent of modifications of either the underlying disease or medication adjustment. Prospective studies using vasopressin antagonists (see the discussion of vaptans below) have shown modest clinical benefits with correction of hyponatraemia. Tolvaptan, a specific vasopressin receptor antagonist, was assessed in a combined randomized prospective

international multicentre study of 448 subjects, the SALT-1 (US cohort) and SALT-2 (international cohort). There was a statistically significant change in one component of a psychological profile test.[25] A planned analysis of scores on the Mental Component of the Medical Outcomes Study 12-item Short Form of the General Health Survey (SF-12) showed improvement. The SF-12, with a range of scores between 7 and 83 (with higher scores indicating better functioning), improved in the combined study, $p = 0.02$. However the changes were significant in the SALT-1 sub-study (US, baseline score 42.3 ± 11.7, treatment effect 3.9, $p = 0.04$) but not in the SALT-2 sub-study (international, baseline score 44.7 ± 12.0, treatment effect 2.2, $p = 0.15$). There were no changes in the physical component summary of the SF-12. The benefits in the SF-12 were more relevant in those with marked hyponatraemia (baseline serum sodium $<130\,\text{mequiv}\,l^{-1}$, $p = 0.04$).[25] Changes in the SF-12 were not considered in the primary outcome analysis and predesigned assessments of gait, balance or cognitive functions were not performed.

Workup and treatment of hyponatraemia

There may be a recognized history of excessive water intake which overwhelms the ability of the kidneys to clear free water, such as primary polydipsia (purposeful intake of 16–20 l of water per day), so-called beer potomania (beer intake of similar volumes) or excessive water intake during prolonged exercise (e.g. in long-distance runners). However, without that history, the usual cause of hyponatraemia is increased water retention, although there may be also a component of solute loss. Tests should be made on the serum for basal metabolic profile (BMP) and measured serum osmolality and on the urine for osmolality and sodium concentration. The BMP will help in the evaluation of acute renal disease (hyponatraemia due to acute tubular necrosis, renal obstruction) and in hyperosmolar pseudo-hyponatraemia due to hyperglycaemia. The serum osmolality will confirm hypo-osmolality (defined as $<275\,\text{mOsm}\,kg^{-1}$) and exclude conditions of pseudo-hyponatraemia due to excess lipids (triglycerides) or hyperosmolar hyponatraemia due to excess circulating osmoles from hyperglycaemia or elevated proteins (macroglobulinaemia). The urine osmolality is usually inappropriately elevated, namely $>100\,\text{mOsm}\,kg^{-1}$, and in many cases higher than the serum osmolality. The urine sodium is usually paradoxically elevated for the apparent serum sodium and is $>30\,\text{mequiv}\,l^{-1}$ and in many cases close to $100\,\text{mequiv}\,l^{-1}$. The cause of the paradoxical natriuresis is not completely understood and may be due to other factors such as elevations in cardiac derived atrial natriuretic peptide (ANP), cardiac or brain-derived brain natriuretic peptide (BNP) or may be due to a direct renal compensatory effect to maintain constant intravascular volume despite hyponatraemia.[1]

The evaluation of hypo-osmolar hyponatraemia should then focus on secondary causes of elevated ADH levels. Decreased effective arterial blood volume (EABV) may be associated with physiologically appropriate elevations in ADH levels which may be inappropriate for serum osmolality. These elevated ADH levels may be corrected by treating the underlying condition. The history and physical examination will help in the determination of volume depletion states (gastrointestinal losses, diuretic losses), low effective arterial blood volume states (orthostatic hypotension due to either primary or secondary adrenocortical insufficiency, hypo-reninaemic hypoaldosteronism), autonomic neuropathic hypotension (Parkinson's disease, multiple system atrophy) or drug-induced states (diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers). In diuretic-induced hyponatraemia, the urinary sodium is usually in a lower range ($<20\,\text{mequiv}\,l^{-1}$) due to the sodium-retaining effect of secondary hyperaldosteronism. Oedema states are those with decreased EABV with hypoalbuminaemia (e.g. cirrhosis, nephrotic syndrome) or decreased perfusion to the carotid baroreceptors resulting from congestive heart failure, cardiac tamponade, negative cardiac inotrophic medications and possibly poor cardiac contractility associated with hypothyroidism. All medications should be reviewed for their potential to cause hyponatraemia (Figure 96.4). Further workup should include evaluation for hypothyroidism (serum TSH) and for both primary and secondary adrenal insufficiency (by cosyntropin stimulation testing).

Other causes of hyponatraemia and more specifically SIADH syndrome include tumours: bronchogenic carcinoma, thymoma; central nervous system lesions: tumours, subarachnoid haemorrhage, neurosurgical procedures; cerebral salt wasting (a possible variant of SIADH syndrome due to acute central nervous system trauma or surgery, associated with hyponatraemia, hypotension and urinary sodium loss); pulmonary disease associated with increased intrathoracic pressure, COPD, positive pressure ventilation; and HIV–AIDS syndromes (which may be associated with relative adrenal or mineralocorticoid insufficiency).

The decision to treat the hyponatraemia depends on the symptoms of neurocognitive dysfunction. Those with serum sodium between 130 and $135\,\text{mequiv}\,l^{-1}$ are usually asymptomatic. If chronic, the hyponatraemia may have allowed time for the development of central nervous system compensation and may not require any therapy. Symptoms of gait disturbances and cognitive impairment found in patients with serum sodium between 125 and $130\,\text{mequiv}\,l^{-1}$ have been shown to improve with correction of hyponatraemia.[24,25] Review and withholding of possible

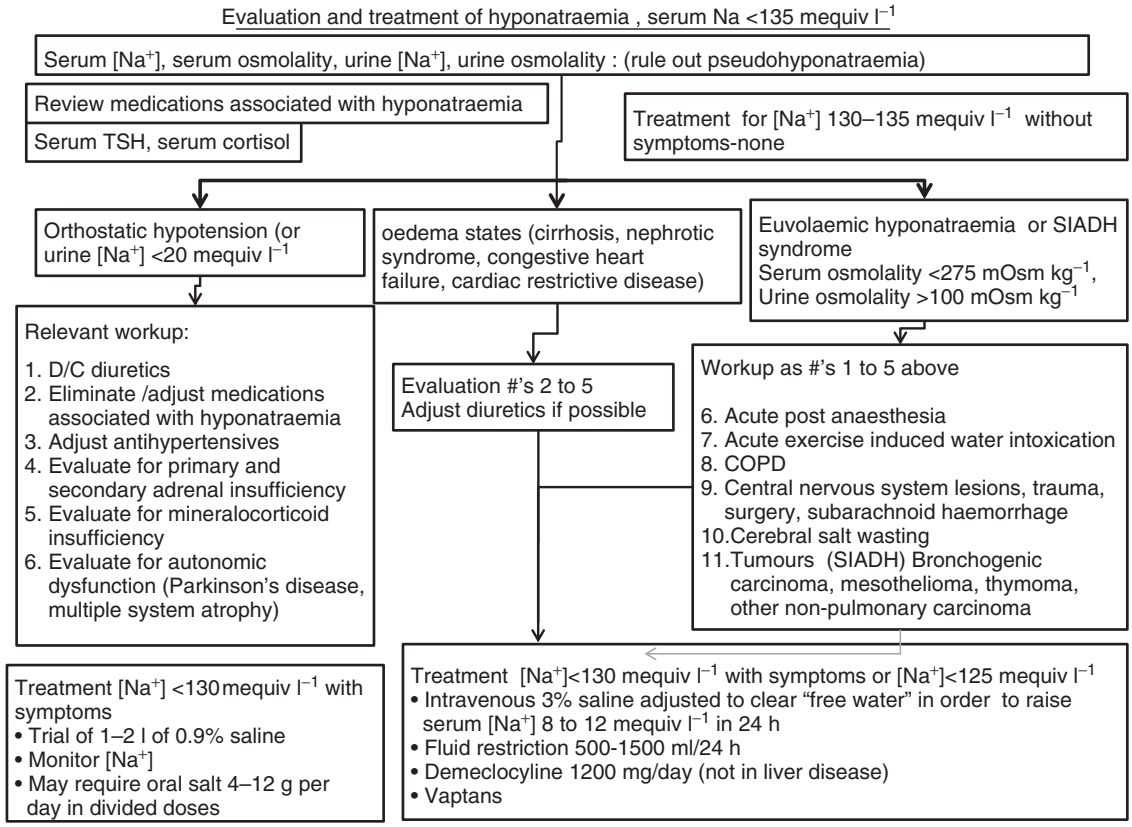

Figure 96.4 Algorithm of workup and therapy for hyponatraemia.

causative medications may be of benefit. Correction of hypothyroidism and hypoadrenalism is mandatory.

If there is orthostatic hypotension or low urine sodium (<20 mequiv l^{-1}), it is presumed that the hyponatraemia is secondary to 'appropriate' physiological vagal stimulation due to low EABV. If the hyponatraemia is diuretic induced, withholding of diuretics or a trial of 1–2 l of intravenous 0.9% saline may partially reverse the hyponatraemia. Usually 0.9% saline will have no effect on a true SIADH syndrome, as the sodium infused is quantitatively lost and the water is retained. If the orthostatic hypotension is due to antihypertensive treatment with excessive blood pressure reduction beyond requirements for the elderly, readjustment of the medication should be performed. If the orthostasis is due to autonomic neuropathy (Parkinson's disease, multiple system atrophy), then cautious use of oral salt 4–8 g per day along with antigravity support stockings may help to correct the underlying low EABV.

Those with serum sodium levels <125 mequiv l^{-1} or with symptoms will need therapy. There are controversies regarding the various protocols for correction of the hyponatraemia as none have been validated in comparative studies.[8] It is agreed that there are two major complications which should be avoided: (1) cerebral oedema due to the delay in correction of hyponatraemia and (2) osmotic demyelination syndrome due to overly rapid correction of the hyponatraemia. The former may occur during states of acute hyponatraemia, that is, in rare occurrences in women or children after general anaesthesia, in athletes with exercise-associated hyponatraemia (over ingestion of water relative to salt loss associated with sweating during prolonged running) or in patients after neurological surgery or subarachnoid haemorrhage.[6] In these situations, delayed correction of serum sodium of only 3–4 mequiv l^{-1} over 24 h has been associated with deteriorating mental state due to cerebral oedema.[6] The osmotic demyelination syndrome, however, occurs due to overly rapid correction of serum sodium, defined as >12 mequiv l^{-1} over 24 h or >18 mequiv l^{-1} over 48 h.

Fluid restriction is indicated for symptomatic euvolaemic and hypervolaemic hyponatraemia and contraindicated in hypovolaemic hyponatraemia. In hypovolaemic hyponatraemia, for example when the hypo-osmolality is due to diuretic or gastrointestinal volume losses, the serum aldosterone and ADH levels are elevated due to physiological responses to the decreased EABV. Infusion of 0.9% saline or the addition of oral salt will correct the serum sodium, since the elevated aldosterone will retain sodium and the increased EABV will lower ADH levels. Infusion of 0.9% saline solution is usually ineffective for euvolaemic and

hypervolaemic hyponatraemia because the hyponatraemia may actually worsen as the infused sodium is quantitatively lost in the urine and the elevated levels of ADH will cause water retention.

In euvolaemic or hypervolaemic hyponatraemia, total fluid restriction between 500 and 1500 ml per day may be required. Symptomatic hyponatraemia with serum sodium $<120\,\text{mequiv}\,l^{-1}$ usually requires correction with intravenous sodium. The concept is to eliminate presumed excess water and restore fluid balance (assuming non-solute losses).[7,8] The treatment plan is to remove a calculated proportion of the free water excess over 24 h to accommodate an increase in serum sodium of 8–12 mequiv l^{-1} and not to correct the serum sodium completely to normal. The formula uses an approximation of for total body water (TBW):

$$\frac{\text{change in free water}}{24\,\text{h}} = TBW \times \left(\frac{[\text{Na}]_{\text{goal}}}{[\text{Na}]_{\text{current}}} - 1\right)$$

where

$$TBW = 0.6 \times (\text{body weight, kg}) \text{ for individuals} < 75\text{years old}$$

or

$$TBW = 0.5 \times (\text{body weight, kg}) \text{ for individuals} > 75 \text{ years old}$$

and

$$[\text{Na}]_{\text{goal}} = [\text{Na}]_{\text{current}} + 10\,\text{mequiv}\,l^{-1}$$

Recommendations for the correction of symptomatic hyponatraemia are therefore made using 3% ($513\,\text{mequiv}\,l^{-1}$) saline solutions. Various protocols have been described,[7,8] although none have been validated or compared with the others. One method is to measure an hourly urine sodium loss in mequiv h^{-1}:

$$\frac{\text{urine volume}\,(\text{ml}\,h^{-1}) \times \text{urine}\,[Na^+]\,(\text{mequiv}\,l^{-1})}{1000\,\text{ml}\,l^{-1}}$$

and replace the sodium loss with the equivalent amount of hypertonic intravenous sodium to maintain a constant intravascular volume. For example, in a 70 kg patient less than 75 years old with a serum sodium of $110\,\text{mequiv}\,l^{-1}$ and with a goal of an increase in serum sodium to $120\,\text{mequiv}\,l^{-1}$ over 24 h, we would attempt to clear free water of $42\,l \times [(120/110) - 1)] = 3.8\,l$ per 24 h. If that person excretes $200\,\text{ml}\,h^{-1}$ of urine with a urine $[Na^+]$ concentration of $100\,\text{mequiv}\,l^{-1}$, then urine sodium losses per hour $= (200\,\text{ml} \times 100\,\text{mequiv}\,l^{-1})/(1000\,\text{ml}\,l^{-1}) = 20\,\text{mequiv}\,h^{-1}$. We would infuse 20 mequiv $[Na^+]$ per hour as 3% saline (40 ml of $513\,\text{mequiv}\,l^{-1}$ solution) with a net hourly loss of free water of (200 ml urine – 40 ml infused) of $-160\,\text{ml}\,h^{-1} = 3.8\,l$ per 24 h.

Alternatively, the 'traditional' correction method has been to calculate the 'theoretical' serum sodium deficit and replace that amount of sodium over 24 h using 3% saline, with the assumption that the infused sodium will re-equilibrate with intracellular water:

$$[\text{Na}]_{\text{required}}, \text{mequiv} = TBW \times ([\text{Na}]_{\text{goal}} - [\text{Na}]_{\text{current}})$$

and

$$\text{volume of 3\% saline infused over 24 h} = \frac{[\text{Na}]_{\text{required}}, \text{mequiv}}{513\,\text{mequiv}\,l^{-1}}$$

The 'traditional' method described above is independent of the urinary losses, although that method may very infrequently require the use of furosemide to promote urinary free water excretion.[7,8]

Medications have been used to assist in free water clearance and may be used in patients with mild symptomatic hyponatraemia in place of fluid restriction or may be used as adjuvants to hypertonic saline infusions in cases of symptomatic euvolaemic or hypervolaemic hyponatraemia. Demeclocycline, in doses as high as 1200 mg per day, may induce nephrogenic diabetes insipidus. Other agents such as lithium, diphenylhydantoin and urea have not been as reproducible or effective.[6]

The newer vaptans allow a further dimension in the therapy of mild symptomatic hyponatraemia. Two vasopressin receptor antagonists are currently approved for use in the correction of euvolaemic and hypervolaemic hyponatraemia[25-27] and two others are under experimental evaluation.[6] The vaptans are non-peptide low molecular weight antagonists of the vasopressin receptor. They bind to an internal domain in the receptor molecule and alter the configuration for normal vasopressin binding and coupling to the internal G protein.[28] Conivaptan is a combined V1a receptor and V2 receptor antagonist and tolvaptan is a selective V2 receptor antagonist. Conivaptan is approved for intravenous administration and tolvaptan is an oral antagonist, but both are to be started in hospitalized patients.[25-27] Conivaptan is administered by intravenous infusion of 20 mg over 30 min followed by 20 mg over 24 h, with the subsequent dose increased to 40 mg per 24 h if required. It is approved only for 4 days. Tolvaptan may be given at 15 mg once daily and may be titrated up as needed once daily to a maximum dose of 60 mg per day. Both drugs are metabolized by the hepatic cytochrome P-450 system of CYP3A and are contraindicated for use with other drugs which are CYP3A inhibitors (clarithromycin, itraconazole, fluconazole, ritonovir and ciclosporin).[27,28] Both drugs have been shown to improved serum sodium with rare increases in the level above the desired $12\,\text{mequiv}\,l^{-1}$ over 24 h. Tolvaptan has been shown to have modest clinical benefits as determined by a quality of life questionnaire in hyponatraemic subjects with serum sodium less than $130\,\text{mequiv}\,l^{-1}$,[25] and in patients with acute congestive heart failure by alleviating feelings of fatigue and dyspnea.[29] Clinical treatment indications for the outpatient management of hyponatraemia with tolvaptan are not well defined and the cost is ~$3000 for 10 tablets.[27]

Workup and treatment of hypernatraemia

Chronic hypernatraemia ($[Na^+] > 145$ mequiv l^{-1}) is associated with extravascular hypertonicity with resultant intracellular dehydration. Clinical presentations may include altered mental status, irritability, hyper-reflexia, tachycardia, orthostasis and dry mucous membranes.[5,7,11] The most clinically significant symptoms are associated with central nervous system dysfunction, ranging from confusion to coma. In extreme cases, the brain dehydration may be associated with vascular rupture and subarachnoid haemorrhage. Chronic dehydration will result in adaptive responses by intracellular generation of organic osmoles. Correction of chronic hypernatraemia must take into account that the overly rapid correction of the hyponatraemia may result in cerebral oedema. Acute management therefore must follow the serum sodium on a regular basis (every 4 h) to adjust the regimen.

Treatment should reverse the underlying causes, such as treating pyrexia, managing gastrointestinal fluid losses and withholding diuretics or lactulose. Correction of the hyperosmolality should then proceed with a goal to decrease serum osmolality incrementally by ~10 mOsm kg^{-1} over 24 h rather than full correction of serum sodium to normal levels.[30] There are various formulas for correction which are usually based on the correction of total body water. The formula for calculating total body water is described above.[7,8,30] One must also supplement for anticipated continuing obligatory water losses (insensible, urinary and gastrointestinal water loss). Obligatory water loss may range from 0.5 to 1.5 l per day of free water. Replacement fluids may include 0.9% saline, 0.45% saline and 5% dextrose in water. If the dehydration is due purely to water without solute loss, the regimen for D5% water may be the easiest to calculate. The concept is similar to treatment of hyponatraemia as described above, except the calculated water deficit is to be added. The calculated free water should reduce the current serum sodium by 10 mOsm kg^{-1} over 24 h.

$$\frac{\text{water replacement}}{24\,\text{h}} = TBW \times \left(1 - \frac{[Na]_{goal}}{[Na]_{current}}\right) + (\text{insensible, gastrointestinal and urinary losses})$$

where

$$[Na]_{goal} = [Na]_{current} - 10\ \text{mequiv}\ l^{-1}$$

In situations where solute is lost in addition to pure water, then 0.45% saline may be a more appropriate intravenous infusion. The infused sodium will stay in the intravascular space to raise the blood pressure. However, the 0.45% saline will correct the osmolality by the 'free water' component, that is, the change in serum sodium per litre of infusate ($\Delta[Na^+]\,l^{-1}$ infusate):[30]

$$\Delta[Na]\,l^{-1}\text{of infusate} = \frac{[Na]_{infusate} - [Na]_{serum}}{TBW + 1}$$

and

$$\frac{\text{volume infused}}{24\,\text{h}} = \frac{\text{desired}\,\Delta[Na]}{\Delta[Na]\,l^{-1}\text{of infusate}}$$

Hence the replacement with 0.45% saline will require approximately twice the rate (or volume) of infusion compared with that calculated for D5% water. Because of the fear that overly rapid correction of the hypernatraemia will cause hyponatraemic cerebral oedema, clinicians are prone to use 0.9% saline for the correction. However, infusion of 0.9% saline, although hypotonic to the existing serum sodium, will not reduce the serum osmolality and may not supply sufficient free water to keep up with obligatory losses. This is explained in detail in the review by Adrogue and Madias.[30] For example, at a serum $[Na^+]$ of 162 mequiv l^{-1} and infusion of 1 l of 0.9% saline (154 mequiv l^{-1}) in a 70 kg person <75 years old, the change in serum sodium per litre ($\Delta[Na^+]_{serum}\,l^{-1}$) of infusate would only be $(-8\ \text{mequiv}\ l^{-1})/42\,l) = -0.2$ mequiv l^{-1} of infusate. It should be noted that there are many assumptions in the calculations for rehydration: that there are no solute losses either before or after the infusion (i.e. the water changes are due to changes in pure water; that the total body water is either 50 or 60%; and that the insensible water losses are between 500 and 1500 ml over 24 h, depending on the underlying illness, such as fever or diarrhoea. It is therefore mandatory to maintain close clinical and laboratory monitoring in order to allow for the large range of assumptions to remain within the desired correction range.

Conclusion

Disorders of water imbalance, hyper- and hyponatraemia, are common in a geriatric population. Among frail elderly patients in long-term care, the incidence of these abnormalities may be as high as 18–63%. Elderly persons, after fluid restriction, have diminished thirst and renal responsiveness to antidiuretic hormone (ADH), but retain their ability to secrete ADH. Hypernatraemia is prevalent in those with Alzheimer's dementia, who have further compromises in both thirst and ADH secretion. Institutionalized frail elderly individuals are often dependent on caregivers for water intake, especially during times of inter-current or febrile illness. Hyponatraemia may be associated with an age-related limitation of renal concentration ability. ADH may be inappropriately elevated due to medications or physiologically increased due to diminished effective arterial blood volume. Hyponatraemia may be associated with comorbidities of falls, bone fractures and death from heart disease, although causality has not been proven. Correction of hypo- and hypernatraemia should be guided by neurocognitive symptoms. In seriously symptomatic

persons or for hyponatraemia ($[Na^+]<125$ mequiv l^{-1}) or hypernatraemia ($[Na^+]>165$ mequiv l^{-1}), adjustments of serum over the ensuing 24 h should be designed to increase the $[Na^+]$ by 8–12 mequiv l^{-1} in hyponatraemia (to avoid osmotic demyelination syndromes) or to decrease the $[Na^+]$ by ~10 mequiv l^{-1} in hypernatraemia (to avoid cerebral oedema). Vaptans are vasopressin antagonists that have been shown to improve serum $[Na^+]$ in hyponatraemia, allow discontinuation of fluid restriction and have exhibited modest effects on quality of life testing. Further studies are necessary to demonstrate the effectiveness of vaptans in the correction of hyponatraemia to improve clinical parameters of gait and neurocognitive function.

Key points

- Older persons have abnormalities in thirst and vasopressin secretion.
- Hyponatraemia is associated with falls and delirium.
- Vasopressin antagonists, vaptans. can be used to treat symptoms of hyponatraemia.

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CHAPTER 97

The pituitary gland

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Introduction

The pituitary gland is the master endocrine gland as it detects and integrates multiple sources of information to regulate physiologic functions (Figure 97.1). The name 'pituitary' originated from the Latin *pituita*, which means mucus; it was believed that the pituitary excreted mucus from the brain through the nose. Understanding age-related changes in this gland and the manifestations of pituitary disease in the elderly is becoming increasingly important as the population ages. The magnitude of these age-related changes is highly variable and the confounding effect of illness on these changes must be appreciated. Interpreting age-associated changes in pituitary function must also take into account the rates and pulsatile secretion of hormones, the rapid changes in the levels of some hormones due to physiological states such as stress, the binding of hormones to plasma proteins, the hormone clearance rates from the plasma and the altered target tissue sensitivity to hormones. The comorbidity often seen in older persons can mask the usual presentation of pituitary disease and make the diagnosis and treatment of these disorders challenging.

This chapter reviews the pertinent changes in the pituitary gland that occur with ageing and the diseases that affect this gland and are relevant to the care of the older individual.

Anatomy

The pituitary gland is functionally divided into an anterior lobe, a posterior lobe and an intermediate lobe. It is located at the base of the brain within the sella turcica and is covered by the diaphragm sella. The pituitary stalk exits through the diaphragm sella to connect with the hypothalamus. The adult pituitary gland weighs 600 mg and measures 13 mm (transverse) × 6–9 mm (vertical) × 9 mm (anteroposteriorly).[1] The optic chiasm is located anterior to the pituitary stalk and is directly above the diaphragm sella, making the optic tracts vulnerable to compression by an expanding pituitary mass. The hypothalamus contains neurons that synthesize releasing and inhibiting hormones and also the hormones arginine vasopressin and oxytocin of the posterior pituitary. The five cell types that secrete hormone in the anterior pituitary gland are listed in Table 97.1.

In the elderly, the pituitary gland is moderately decreased in size and contains areas of patchy fibrosis, local necrosis, vascular alterations and cyst formation. Extensive cellular deposits of lipofuscin and regional deposits of amyloid are also seen. There are no prominent age-associated alterations in the relative proportions of different types of pituitary secretory cells. The LH and FSH contents are somewhat increased in older people, but there are no age-related changes in the pituitary content of GH, PRL and TSH.[2]

Blood supply

The blood supply to the anterior pituitary is through a rich vascular network. The superior hypophyseal arteries (from the internal carotid arteries) supply the hypothalamus and form a capillary network and portal vessels from this network supply the anterior pituitary. These vessels form the conduit for the releasing and inhibiting hormones of the hypothalamus to the anterior pituitary cells. Inferior hypophyseal arteries from the posterior communicating and internal carotid arteries supply the posterior pituitary. Drainage is into the cavernous sinus and internal jugular veins.

Anterior pituitary disorders – clinical manifestations

Pituitary tumours are very common, occurring at postmortem in 20–25% of persons.[3] Microadenomas are more common in men than in women and over half of the tumours in older persons have immunoreactive prolactin

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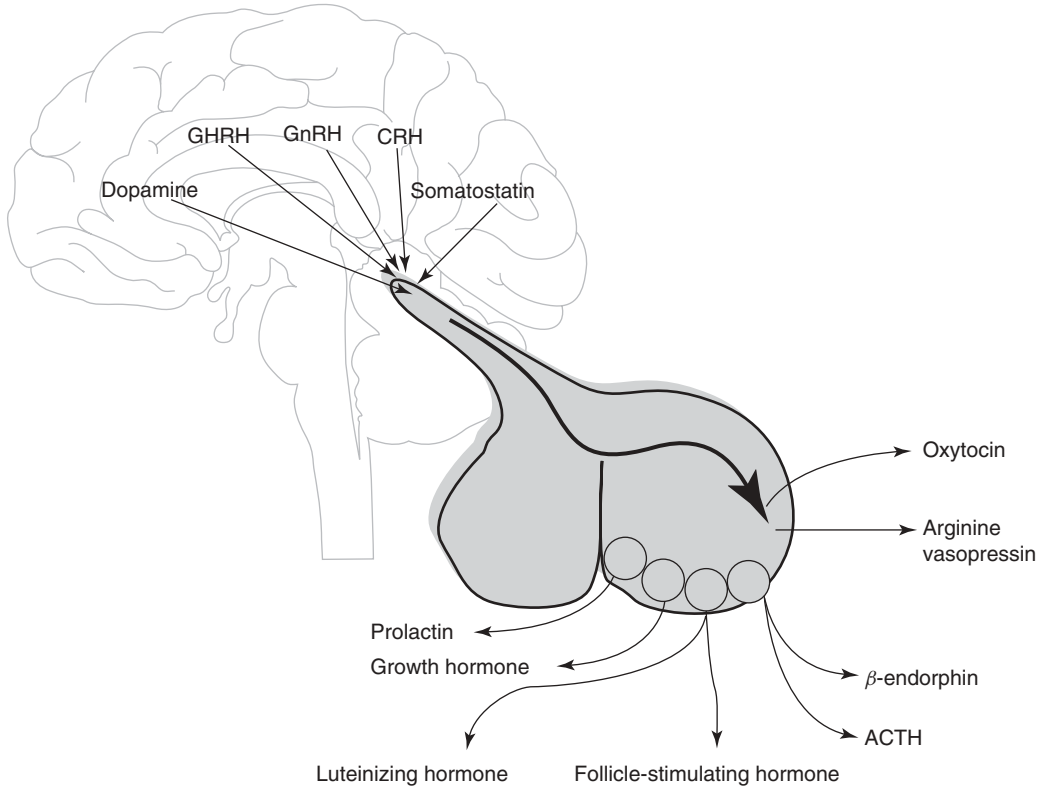

Figure 97.1 Hormones produced by the anterior pituitary and its hypothalamic controlling factors.

Table 97.1 Pituitary cell types, their hormones and their percentages[a].

Cell type	Hormone	Stimulators	Inhibitors	Percentage of anterior pituitary cells
Corticotroph	POMC including ACTH	Corticotropin-releasing hormone, vasopressin, cytokines	Glucocorticoids	15–20
Somatotroph	GH	GH-releasing hormone, GH secretagogues	Somatostatin, IGF	50
Thyrotroph	Alpha subunit and beta subunit (thyrotropin)	TRH	T3, T4, dopamine, somatostatin, glucocorticoids	<10
Gonadotroph	FSH and LH	Gonadotropin-releasing hormone	Sex steroids, inhibin	10–15
Lactotroph	PRL	Estrogen, TRH	Dopamine	10–25

[a]POMC, pro-opiomelanocortin peptides; ACTH, adrenocorticotrophic hormone; GH, growth hormone; FSH, follicle-stimulating hormone; LH, leuteinizing hormone; PRL, prolactin; TRH, thyrotropin-releasing hormone; IGF, insulin-like growth factor; T3, triode thyronine; T4, thyroxine.

staining in their cytoplasm. Despite the frequency of this occurrence, pituitary tumours in the elderly are a neglected subject in the literature. Outcome studies on the prevalence and treatment of the various types of pituitary adenomas are confounded by lack of long-term follow-up, comorbidity and a referral bias towards younger patients.[4] Pituitary tumours in persons over 60 years of age account for 3–13.4% of all brain tumours.[5] Pituitary lesions present with a variety of manifestations, including pituitary hormone hyper- and hyposecretion, enlargement of the sella turcica and visual loss. In the general adult population, hypersecreting pituitary adenomas are the most common cause of pituitary dysfunction and the earliest symptoms are due to endocrinological abnormalities. Visual loss and headache are later manifestations and are due to sellar enlargement. These later symptoms are seen only in patients with

large tumours on extension above the sella.[6] Early visual symptoms include the hemifield slide phenomenon, that is, images floating apart from one another and the inability to focus on two points at the same time, for example, the inability to do needlework. The classical visual sign of pituitary tumours is bitemporal hemianopsia. In older persons, this sign can be difficult to detect as some degree of bitemporal hemianopsia occurs as a normal part of the ageing process.

In contrast, most clinically relevant pituitary tumours in the elderly are non-functioning and do not present with features of hormonal hypersecretion. Patients are more likely to be diagnosed with visual field deficits or as incidentalomas.[4] In a study by Cohen *et al*.,[7] 73% of 22 pituitary tumours diagnosed in patients over 70 years of age were non-functioning. Cushing's disease was diagnosed in one, prolactinoma in one and acromegaly in three. In the series by Kleinschmidt-DeMasters *et al*.,[5] of the 13 tumours one was a prolactinoma with subarachnoid haemorrhage and apoplexy and two secreted growth hormone. The other 10 were non-functioning.

Of the hormones hypersecreted by pituitary adenomas, prolactin (PRL) is the most common. Measuring PRL is an important part of the evaluation of patients with suspected pituitary disorders and should be performed in older patients presenting with gonadal dysfunction, secondary gonadotropin deficiency or sella turcica enlargement. The characteristic syndromes of acromegaly and Cushing's disease are due to the hypersecretion of GH and ACTH, respectively, but are rare presentations of pituitary disease in the older population. The characteristic symptoms of acromegaly are given in Table 97.2. Even more rarely, ectopic GH-releasing hormone causing somatotroph hyperplasia leading to acromegaly and corticotropin-releasing hormone to Cushing's disease can be due to abdominal or chest tumours.

Hypopituitarism is another manifestation of a pituitary adenoma. The clinical presentation of hypopituitarism depends on which hormones are affected, the acuteness or chronicity of the disorder and the severity of the hormone deficiencies (Table 97.3).

In adults, hypogonadism is the earliest clinical manifestation of an adenoma and is secondary to elevated PRL, ACTH and cortisol or GH. The hypogonadism is due to impaired secretion of gonadotropin-releasing hormone rather than anterior pituitary distinction. Older persons with hypopituitarism may present with recurrent falls,[8] hyponatraemia,[9] postural hypotension and hypothyroidism with an inappropriately suppressed TSH.[10] Tayal *et al*. reported pituitary adenomas as the most common cause of hypopituitarism in 12 patients aged 63–89 years.[11] The presenting features in this series were lethargy, hypotension, weakness, falls, weight loss, drowsiness, confusion, immobility and urinary incontinence. Other symptoms of hypopituitarism in older adults include changes in body composition (abdominal obesity and loss of muscle leading to decreased exercise tolerance and fatigue – due to GH loss), decreased sexual function (owing to gonadotropin loss), hypoglycaemia and hypocortisolism (caused by loss of ACTH), polyuria and polydipsia (due to deficits in vasopressin). Other causes of hypopituitarism are given in Table 97.4.

Pituitary apoplexy, resulting from haemorrhage or infarction of the pituitary gland, usually occurs as a

Table 97.2 Symptoms of acromegaly in older persons with pituitary secreting. tumours[a].

Fatigue
Weakness
Swelling of hands and feet
Coarse facial features
Increased head size
Increased perspiration
Deepening of voice
Enlargement of lip, nose and tongue
Joint pain
Snoring
Cardiomyopathy
Headaches
Visual loss

[a]The diagnosis can often be made by looking at serial photographs taken over the lifetime to detect the physical changes that occurred.

Table 97.3 Symptoms of hypopituitarism in older adults.

Insufficient thyroid-stimulating hormone production
• Confusion
• Cold intolerance
• Weight gain
• Dry skin
• Constipation
• Hypertension
• Fatigue
Insufficient growth hormone production
• Fatigue
• Decreased strength
Insufficient gonadotropin production
• Fine wrinkled skin
• In males, worsening libido
Insufficient corticotropin production (very rare)
• Fatigue
• Hypoglycaemia
• Hypotension
• Intolerance of stress

Table 97.4 Causes of hypopituitarism.

Primary hypopituitarism
• Pituitary tumours
• Hemosiderosis
• Infections
• Sarcoidosis
• Radiation therapy
• Tuberculosis
• Hypophysitis (autoimmune disease)
• Surgery
• Impaired vascular supply
Secondary hypopituitarism
• Hypothalamic tumours
• Head injuries
• Multiple sclerosis
• Inflammatory disease

sudden crisis in a patient with a known or previously unrecognized pituitary tumour, but may occur in a normal gland. The risk factors for this condition are common in the elderly. Symptoms at presentation include the sudden onset of headache, stiff neck, oculomotor disturbances and confusion.[4]

An enlarged sella turcica is another presentation of pituitary disease. The enlargement is usually noted on X rays performed for other indications such as trauma, sinusitis or mental status changes. Patients with an enlarged sella usually have a pituitary adenoma or empty sella syndrome as the cause.[6] In the elderly, carotid artery aneurysms would also be in the differential diagnosis, whereas craniopharyngiomas and lymphocytic hypophysitis seen in younger populations would be less likely. Pituitary function in the empty sella syndrome is usually normal, although some patients have hyperprolactinaemia. MRI confirms the diagnosis.

An increased suspicion of a pituitary/hypothalamic disorder should occur if patients present with unexplained unilateral or bilateral visual field deficits including bitemporal hemianopsia or visual loss. Vision changes were the most common presentation of pituitary adenomas in Cohen *et al*.'s series of 22 patients aged 70 years and over.[7] These patients should have a neuro-ophthalmological evaluation, MRI and a serum prolactin, and also an assessment for hypopituitarism. Additional concerns for large pituitary lesions are that they may have lateral extension into the cavernous sinus, leading to diplopia caused by dysfunction of the third, fourth or sixth cranial nerve. These large tumours may also extend in an inferior direction through the sphenoid sinus and roof of the palate and lead to cerebrospinal fluid leakage. Seizures and personality changes can result from invasion of the temporal or frontal lobe. Hypothalamic encroachment can lead to hypogonadism, diabetes insipidus and disorders of temperature regulation, appetite and sleep. Headaches can be due to stretching of the dural plate and do not necessarily correlate with size or extension of the mass.

Anterior pituitary disorders – treatment

Non-functioning pituitary tumours

The clinical features of these tumours are usually due to mass effects. Hypopituitary and hyperprolactinaemia (caused by impingement on the pituitary stalk and interference with tonic inhibition of lactotroph cells by dopamine secreted by the hypothalamus) are usually present in varying degrees. Less than one-third of the time there is an elevation of follicle-stimulating hormone (FSH), LH or their subunits. In one series of 27 patients, aged 65–81 years, there was global anterior hypopituitarism in 33% and partial hypopituitarism in 37% of patients.[12]

There is no effective medical therapy. Non-functioning microadenomas ($\leq$ 10 mm) have a benign natural history and can be followed with annual visual acuity and visual field testing and neuroimaging in the asymptomatic patient. Surgery and radiotherapy appear to be very effective in producing control of symptomatic non-functioning pituitary tumours. In Cohen *et al*.'s series,[7] transsphenoidal surgery was performed in 64% of the 16 patients and was well tolerated with few postoperative complications. Vision was significantly improved in seven and unchanged in one. Temporary visual deterioration occurred in one patient and permanent deterioration occurred in another. In Brada *et al*.'s population aged 60 years and over, 79% of patients treated with radiotherapy had a diagnosis of non-functioning pituitary adenoma and, after 10 years of follow-up, only one showed evidence of tumour progression.[13] In one series of macroadenomas, only 31% faced total removal of the tumour.[12] One-third required radiotherapy.

In the USA, 5497 pituitary surgery operations were performed between 1996 and 2000. There was a 0.6% death rate and a 3% discharge to long-term care. Age was a significant predictor of mortality and a worse outcome at hospital discharge.[14] Surgeons with a higher case load had much better outcomes.

Prolactinomas

In addition to symptoms caused by mass effects, postmenopausal women may present with galactorrhoea and men can present with hypogonadism including decreased libido. Excluding medications, hypothyroidism and other causes of hyperprolactinaemia is an important step in the initial approach to this problem. In general, treatment consists of medical therapy with a dopamine agonist. The available dopamine agonists include bromocriptine,

lisuride, pergolide and cabergoline. Dopamine agonists can produce orthostans and delirium with hallucinations and delusions. Surgery is used for those intolerant or resistant to dopamine agonist therapy. Surgery is also indicated for those patients who require urgent decompression of the sella turcica for visual field deficits. Treatment is recommended for microprolactinoma ($\leq$ 10 mm) to prevent osteoporosis, the infrequent occurrence of tumour progression and the effects of prolonged hypogonadism.

The management of prolactinomas in the elderly is hindered by a lack of data. Several reviews included no elderly patients,[15–17] so extrapolation from data in younger populations and individualizing treatment decisions are necessary.

Cushing's disease

The diagnosis of Cushing's disease may be more challenging in the elderly because symptoms [weight gain, hypertension (HTN), diabetes mellitus (DM)] may be nonspecific and because elevated urinary cortisol exertion can be seen with Alzheimer's disease and multi-infarct dementia.[18] Lack of cortisol suppression after low-dose dexamethasone is seen with depression and Alzheimer's disease in addition to Cushing's disease and further complicates the diagnosis. In addition, up to 50% of ACTH tumours are not visible on MRI and require inferior petrosal sinus sampling and CRH-provocative testing.

Treatment of ACTH-producing tumours is by transsphenoidal resection. A higher relapse rate has been seen in younger than older patients.[19,20] Metyrapone has also been used to treat Cushing's disease in the elderly.[21]

Acromegaly

The predominant cause of acromegaly is GH-producing tumours and the effects of GH are medicated by insulin growth factor-1 (IGF-1) (produced by the liver). Symptoms are those of acromegaly plus those caused by mass effects of the tumour. The best screening test for this disease is an IGF-1 level. Because of secretion of GH is pulsatile, random levels are not helpful with the diagnosis. The treatment of choice for a GH-secreting tumour is excision. Pharmacological therapy with octreotide or radiotherapy can be considered if the disease persists after excision. Pegvisomant, which blocks the effect of growth hormone on its receptor, may be appropriate in some persons with oversecretion of growth hormone.

Acromegaly in older patients appears to be a milder disease than in younger patients,[22] and it has been suggested that treatment can be more conservative in this group.[23] It appears that elderly individuals respond well to both transsphenoidal surgery and medical treatment with somatostatin agonists.[4]

Thyrotropin (TSH)-secreting tumours

About 2% of all pituitary tumours are TSH-secreting. They can present with symptoms of thyrotoxicosis. Among 25 patients with TSH-producing tumours, one was 60, one 63 and one 80 years old.[24] There are few data on treatment in any age groups for this rare tumour. Octreotide appears to be a safe and effective treatment.[25] However, in older patients tumours tend to be large, requiring surgery and radiation. Often some tumour remnant remains in these patients.

Gamma-knife radiosurgery

Gamma-knife radiosurgery is a recent option for the management of pituitary tumours. The gamma-knife is a device that allows radiation to be delivered from outside the head to a precise position within the brain. It requires no incision. Multiple radiation beams are aimed at the pituitary. Each individual beam is too weak to damage the brain tissue through which it passed, with the tissue destruction happening only at the place in the pituitary where the beams meet. Accuracy is to within a fraction of a millimetre. Occasionally, gamma-knife therapy can cause local swelling 2–12 months following the procedure. Otherwise, it is relatively free of side effects.

Empty sella turcica

Empty sella turcica has been diagnosed in men and women in their 60s and 70s. It is characterized by enlargement of the bony structure enclosing the pituitary together with loss of pituitary tissue. It occurs most commonly in overweight women with high blood pressure. Symptoms include cephalgia, hypopituitarism or a runny nose. Most empty sellas are diagnosed incidentally during a radiological procedure of the head.

Anterior pituitary hormone secretion – functional changes with age

Functional changes in anterior pituitary hormone secretion occur with increasing age. Table 97.5 summarizes some of the changes that have been reported in these hormone.[26] Older persons with traumatic brain injury due to motor vehicle accidents or falls can lead to pituitary insufficiency.[27,28] Hypopituitarism in older persons is most commonly associated with macroadenomas and less commonly with an empty sella or pituitary hyperplasia.[29] Presenting symptoms included visual field defects, asthenia, memory or gait impairment, nausea and depression. Surgery and radiation are safe in this population.

Table 97.5 Changes reported in hormones.

Hormone	Increase	Decrease	None
Adrenocorticotrophin hormone	−	+	−
Follicle-stimulating hormone	+	+	−
Luteinizing hormone	+	+	−
Growth hormone	−	+	−
Thyroid-stimulating hormone	−	+	+
Prolactin	+	+	+

Gonadotropins (LH and FSH)

Blood concentrations if both LH and FSH increase abruptly and universally in about the sixth decade in women as ovarian secretion of estrogens decreases. These values gradually decline after age 75 years.[30] Serum FSH and LH rise approximately twofold in men aged 75–85 years and then decline gradually, as pituitary gonadotropic secretory capacity is reduced with advancing age. This is suggested by a decrease in the amplitude of LH and/or FSH responses to gonadotropin-releasing hormone.[31] There is a wide spread of values at these ages, suggesting primary hypogonadism in some men and secondary (central) hypogonadism in others. Secondary hypogonadism may be the rule rather than the exception with ageing.[32] The mean LH pulse amplitude and the maximum pulse amplitude are lower in elderly than in younger males.[33]

The changes in the LH response to ageing may be due to the effects of ageing on the catecholamine responses in the hypothalamus. The oestrous cycle in old female rats is reinstated by drugs that stimulate brain catecholamine neurotransmitters.[34] Naloxone administered to old rats partially restores the LH surge. This suggests that opiates from the hypothalamus may be partly responsible for reduction in LH secretion.[36]

Prolactin (PRL)

Unlike other pituitary hormones, hypothalamic control of prolactin is mainly inhibitory through dopamine. Other than simulating lactation in the post-partum period, prolactin has no significant physiological function. Hyperprolactinaemia suppresses sex steroid production.

There is no consensus on the effects of ageing on prolactin secretion. Investigators have reported decreases, increases or no change in prolactin changes.[2] Sawin *et al.*'s analysis of prolactin levels from the Framingham cohort showed no significant difference in the prolactin levels between the age-matched genders.[36] The mean prolactin level in men for ages 40–49 years was 6.4 ± 3.1 mg ml^{-1} compared with 8.4 ± 3.8 mg ml^{-1} for ages 80–89 years. In age-matched women, the values of 6.9 ± 3.1 and 8.8 ± 5.3 mg ml^{-1} corresponded to the same age groups as described for the men. Alterations of PRL in humans are probably of small magnitude and unlikely to affect sexual function in the older adult, but more likely the cause of hyperprolactinaemia in this population are medications and prolactinomas, which should be evaluated.[37]

Growth hormone

Both ageing and gender affect growth hormone secretory dynamics. Young women have twice as high daily growth hormone production as young men. The fall in growth hormone over the life span is from 1200 μg m^{-2} in adolescents to 60 μg m^{-2} in older individuals.[38] The fall in growth hormone secretion with ageing is due both to a decrease in the orderly production of growth hormone releasing hormone from the hypothalamus and to an increase in somatostatin production from the hypothalamus. The fall in growth hormone secretion leads to a decline in IGF-1.

Circulating growth hormone is bound to growth hormone-binding proteins. With ageing there is a decline in growth hormone-binding proteins. The level of growth hormone-binding proteins is approximately half that in nonagenarians compared with 60-year-olds.[39]

In older women, estrogen increases growth hormone secretion. In older men, only high doses of an aromatizable form of testosterone (200 mg) increased basal and the mytohemeral growth hormone production.[40]

Overall ageing is associated with multiple changes of the hypothalamic growth hormone–IGF-1 axis and their binding proteins. Interactions with sex hormones further complicate these effects. However, studies with growth hormone or ghrelin analogue replacement have failed to demonstrate physiologically important effects of these changes on the ageing process.

Posterior pituitary gland

The posterior pituitary gland is neural tissue and consists only of the distal axons of the hypothalamic magnocellular neurons. The cell bodies of these axons are located in the supraoptic and paraventricular nuclei of the hypothalamus. The axon terminals contain neurosecretory granules

Table 97.6 Causes of diabetes insipidus.

Hypothalamic malfunction or damage
Brain injury including cerebrovascular accidents
Tumours
Meningitis and encephalitis
Sarcoidosis
Tuberculosis

in which are stored the hormones oxytocin and vasopressin [antidiuretic hormone (ADH)]. Diseases of the posterior pituitary (diabetes insipidus, syndrome of inappropriate ADH) modulate water homeostasis. Persons with diabetes insipidus (insufficient production of vasopressin) present with excessive thirst, polyuria and dehydration. The major causes of diabetes insipidus are listed in Table 97.6.

Water excretion in the elderly is affected by physiological changes of the ageing process and leads to an increased risk of both hyponatraemia and hypernatraemia.[41,42] Multiple diseases common in elderly persons and the treatments for these diseases can further affect water balance. In addition, body water is reduced in the elderly. By age 75–80 years, total body water declines to 50% of the level in young adults and complicates studies of responses to dehydration, volume stimulation and osmolar stimulation.[43]

There is a reduced responsiveness of the renal collecting duct to vasopressin in older than younger individuals, the consequence of which is an increased vulnerability to water deprivation.[44] This decreased renal sensitivity to ADH is thought to be due to a decreased ability of vasopressin to stimulate aquaphorin-2 levels in the kidney and results in a chronic increase in vasopressin secretion and an eventual depletion of posterior pituitary hormone stores. This may cause a decreased visualization of the bright spot on T1-weighted MRI scans in elderly people.[45] The bright spot in the sella on MRI is due to stored hormone in neurosecretory granules in the posterior pituitary.

Vasopressin levels have a greater range of normal in older persons and do not correlate as directly with plasma osmolality.[46,47] Changes in vasopressin levels in response to osmotic stimulation are either normal[48] or increased,[48,49] while the vasopressin response to volume depletion (mediated by baroreceptors) is increased.[50]

Older persons also have a decrease in thirst in response to osmotic stimulation. As a result of the decrease in thirst and in the responsiveness of the kidney to vasopressin, it is easy for older patients to become dehydrated and hypernatraemic despite an increase in vasopressin secretion.[51] Even when recovering from dehydration, older people drink less fluid to return their volume to normal.[52]

Excreting a water load is also limited in the elderly. Decreases in glomerular filtration rate and a decreased suppression of vasopressin contribute to this phenomenon. Vasopressin is not shut off in the elderly as well as in the young in response to drinking and oral–pharyngeal receptor stimulation. Those older patients with increased levels of ADH secretion in response to a particular osmotic level have a downward alteration in their osmotic set point. This inability to execute a water load can lead to an increased tendency towards hyponatraemia in the elderly. Almost 75% of patients with the syndrome of inappropriate ADH secretion are over 65 years of age.[37]

Given the issues raised above by numerous studies, healthy older adults probably exhibit normal secretion of vasopressin but do have a decreased thirst appreciation and a decreased ability to maximally concentrate the urine to retain water or to maximally dilute the urine to excrete water. Both hyponatraemia[53] and hypernatraemia,[54] to which older people are susceptible due to the physiological changes noted above, can cause increased morbidity and mortality, especially in the frail elderly, and therefore warrant vigilance for their occurrence.

Key points

- Non-functioning pituitary tumours are extremely common in older persons.
- With ageing there is a decline in anterior pituitary function.
- Diabetes insipidus is due to insufficient production of vasopressin and leads to excessive thirst and polyuria.
- Treatment for pituitary tumours includes medical, surgery and most recently gamma-knife radiation.

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CHAPTER 98

Thyroid disorders

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Introduction

Thyroid disorders are more common in older than in younger people, especially in women, and they are frequently undiagnosed.[1–3] Several changes in the thyroid function and laboratory tests arise with ageing. The understanding of these modifications may help to differentiate age-related physiological changes, subclinical dysfunction and overt disease, especially in the difficult decision of whether to start treatment or avoid it in subclinical dysfunction, which has long been a matter of controversy. In the past years, several reports have linked subclinical dysfunction with changes in cognition and cardiovascular risk, hence it is key to know how to identify correctly the subjects at true risk.[4–6] It is also possible that subtle thyroid alterations in younger people may evolve to overt clinical manifestation during ageing. For example, non-toxic goitre starting as a diffuse thyroid enlargement during early life may acquire nodularity and autonomous function with ageing and may progress, although not frequently, to toxic nodular goitre. Before becoming clinically apparent, chronic thyroiditis and toxic goitre may exhibit only slight laboratory modifications corresponding to subclinical states of hypothyroidism or hyperthyroidism. Nevertheless, only a portion of patients with subclinical laboratory dysfunction progresses to overt disease, hence it is essential to identify the patients at risk who merit treatment.

Even if thyroid dysfunction is more common in older than younger populations, it is frequently overlooked. The main reason why thyroid disorders in older persons often escape clinical detection is because their signs and symptoms often mimic age-associated functional changes or disease of other organs. For example, hypothyroidism may induce or worsen cognitive and physical decreased functions, constipation, cold intolerance, body weight gain, anaemia or lipid disorders, all frequently observed in euthyroid elders. Similarly, thyroid hyperfunction may be manifested as arrhythmia and congestive heart failure, which may well be interpreted as the manifestation of cardiac disease, very frequent at this age. Body weight loss associated with thyroid hyperfunction may be interpreted as part of the normal ageing process, undernutrition or neoplasia, also frequent in old age. In addition, thyroid hyperfunction may be asymptomatic or 'apathetic', presenting merely with subtle signs, again frequently misinterpreted as normal age-associated changes in different organ systems or as a reduced thyroid function.[1,3,5,6] In fact, older people may have similar manifestations that correspond to increased or decreased function, such as mental confusion, depression, falling, walking disturbances, urinary incontinence from immobility, congestive heart failure, constipation or diarrhoea. These signs also correspond to other disorders commonly observed in older people. The correct identification of thyroid disorders is critical in older persons, since they can significantly impact the quality of life, either because of the thyroid disorder itself or because of worsening of an underlying disease or impaired function. The existence of other diseases and the use of multiple medications may further mask or mimic the presentation of thyroid disease.

The lack of evident clinical manifestations of thyroid dysfunction in the elderly calls for a detailed clinical evaluation and a high index of suspicion to identify their presence, with the appropriate confirmation by means of reliable laboratory testing. Nevertheless, thyroid tests may also have minimal changes with age and caution in the interpretation of such changes is warranted.

This chapter explores the changes in thyroid function and disease in older age, highlighting the most common thyroid problems in this period of life, including overt and subclinical hypothyroidism and hyperthyroidism, non-thyroidal illness and the approach to thyroid nodules.

Age-related modifications in thyroid function

Several subtle changes occur in the thyroid function with advancing age, but the interpretation of the altered

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findings in laboratory parameters is not easy because they are modified by several factors. Studying age-related changes in old age without confounders is cumbersome because an adequate sample of healthy elders is difficult to find. The variability of modifications reported in different studies is probably due to selection bias.[1] The main confounders include chronic non-thyroidal illness (NTI, see below), polypharmacy (Tables 98.1–98.3) and the increased prevalence of autoimmune subclinical hypothyroidism. It seems that the modifications that persist after taking into account these confounders include an age-dependent decrease in TSH, a decreased triiodothyronine (T3) and an increase in the inactive metabolite reversed T3 (rT3) with an apparent unchanged circulating concentration of total and free thyroxine (T4). Deiodination in the outer ring, responsible for the conversion of T4 into T3, decreases with age and seems to be a plausible explanation for the decreased concentration of T3 and the increase in rT3.[1,7,8] Recently, an increased inner ring deiodination, resulting in an elevated clearance of T4 and T3 and an augmented production of rT3, was proposed to contribute to these changes and mediate NTI.[9]

Table 98.1 Agents that inhibit thyroid hormone synthesis and secretion.

Block iodide transport into the thyroid gland
Monovalent anions (SCN^-, ClO_4^-, NO_3^-)
Complex anions (monofluorosulfonate, difluorophosphate, fluoroborate)
Minerals (bromine, fluorine)
Lithium
Ethionamide
Impair TG iodination and iodotyrosine coupling
Propylthiouracil, methimazole, carbimazole
Sulfonamides
Sulfonylureas
Salicylamides
Resorcinol
Aminoglutethimide
Amphenone
Thiocyanate
Antipyrine
Aminotriazole
Amphenidone
2,3-Dimercaptopropanol
Ketoconozole
Inhibitors of thyroid hormone secretion
Iodide (in large doses)
Lithium
Mechanism unknown
p-Bromdylamine maleate
Phenylbutazone
Minerals (calcium, rubidium, cobalt)
Interleukin II
γ-Interferon

Source: adapted from L. DeGroot, http://www.thyroidmanager.org.

Table 98.2 Compounds that affect thyroid hormone transport proteins in serum.

Increase TBG concentration	*Decrease TBG concentration*
Estrogens	Androgens and anabolic steroids
Heroin and methadone	Glucocorticoids
Clofibrate	L-Asparaginase
5-Fluorouracil	Nicotinic acid
Perphenazine	
Interfere with thyroid hormone binding to TBG and/or TTR	
Salicylates and salsalate	
Diphenylhydantoin and analogues	
Furosemide	
Sulfonylureas	
Heparin	
Dinitrophenol	
Free fatty acids	
Phenylbutazone	
Halofenate	
Fenclofenac	
Orphenadrine	
Thyroid hormone analogues	

Source: adapted from L. DeGroot, http://www.thyroidmanager.org.

The age-related decrease in TSH and thyroid hormones indicates the presence of a partial central hypothyroidism. However, Hollowell *et al*. reported an increased TSH with ageing in a large population including persons without circulating thyroid autoantibodies and without other risk factors for thyroid dysfunction.[10] Another possible confounder of the uneven results of different studies is the dissimilar iodine intake and diverse prevalence of subclinical thyroid disease in the examined populations. Whether age-associated changes in thyroid function contribute to the ageing process itself is not yet established.

The high prevalence of NTI (discussed below) among older people due to the presence of chronic illness and/or malnutrition is a major confounder in the evaluation of thyroid function in old age.[1] In a recent study evaluating ambulatory men, those with NTI – low serum T3 and a high serum rT3 – were older and had more comorbidity (i.e. diabetes, osteoarthritis, hypertension, congestive heart failure and chronic obstructive pulmonary disease) compared to subjects without NTI.[11] High rT3 was associated with a low performance score independent of the presence of disease.

The use of multiple medications, a hallmark in old populations, may also influence thyroid function tests. Drugs can inhibit thyroid hormone synthesis and secretion (Table 98.1), affect thyroid hormone transport proteins in serum (Table 98.2) and alter the extrathyroidal metabolism of thyroid hormone (Table 98.3). Pharmacological agents can induce hypothyroidism (e.g.. lithium, amiodarone),

Table 98.3 Agents that alter the extrathyroidal metabolism of thyroid hormone.

Inhibit conversion of T4 to T3
Propylthiouracil
Glucocorticoids
Propranolol
Iodinated contrast agents
Amiodarone
Clomipramine
Stimulators of hormone degradation or faecal excretion
Diphenylhydantoin
Carbamazepine
Phenobarbital
Cholestyramine and colestipol
Soybeans
Rifampin
Ferrous sulfate
Aluminium hydroxide
Sucralfate
Increase serum TSH concentration and/or its response to TRH
Iodine and iodide-containing compounds (i.e. expectorants, anti-arrhythmic and anti-anginal agents)
Lithium
Dopamine receptor blockers (metoclopramide, domperidone)
Dopamine-blocking agent (sulpiride)
Decarboxylase inhibitor (benserazide)
Dopamine-depleting agent (monoiodotyrosine)
L-Dopa inhibitors (chloropromazine, biperidine, haloperidol)
Cimetidine
Clomifene
Spironolactone
Amphetamines
Decrease serum TSH concentration and/or its response to TRH
Thyroid hormones (T4 and T3)
Thyroid hormone analogues (D-T4, 3,3′,5-Triac, etiroxate·HCl, 3,5-dimethyl-3-isopropyl-L-thyronine)
Dopaminergic agents (piribedil, apomorphine, lisuride)
Dopamine antagonist (pimozide)
Dopamine
L-Dopa
2-Bromo-α-ergocryptine
Fusaric acid (inhibitor of dopamine β-hydroxylase)
Pyridoxine (coenzyme of dopamine synthesis)
α-Noradrenergic blockers (phentolamine, thioridazine)
Serotonin antagonists (metergoline, cyproheptadine, methysergide)
Serotonin agonist (5-hydroxytryptophan)
Glucocorticoids
Acetylsalicylic acid
Growth hormone
Somatostatin
Octreotide
Opiates
Clofibrate
Fenclofenac

Source: adapted from L. DeGroot, http://www.thyroidmanager.org.

hyperthyroidism (e.g. amiodarone, iodine) and abnormal thyroid function tests by affecting thyroid-binding globulin (TBG) status (e.g. estrogens, glucocorticoids) or the binding of T4 to TBG (e.g. heparin); they can suppress T4 to T3 conversion (e.g. amiodarone, glucocorticoids, propranolol) or suppress TSH secretion (e.g. dopamine, glucocorticoids). The use of multiple medicaments is the rule in older patients and interactions among the different agents may have unknown effects on thyroid function.

Thyroid autoantibodies, including anti-thyroperoxidase and anti-thyroglobulin autoantibodies, increase with age, particularly in females over 60 years of age.[1,10] In the Whickham survey, the incidence of anti-thyroglobulin and anti-microsomial autoantibodies was 7 and 9% in females over 75 years of age compared with 2 and 5% in total population, respectively.[12] However, the prevalence of clinically overt autoimmune thyroid disease is not greater in older than younger groups. The increased TSH levels in elders shown in some studies[12,13] is probably due to the inclusion of women with a high titre of thyroid antibodies and/or subclinical hypothyroidism. The prevalence of thyroid autoantibodies was shown to be higher in subjects aged 70–85 years compared with people younger than 50 years, with centenarians having a similar prevalence to that of young subjects (<50 years old).[14] The prevalence of thyroid autoantibodies was higher in unselected or hospitalized elderly patients than centenarians, suggesting that the appearance of thyroid autoantibodies might be related to age-associated disease, rather than to the ageing process *per se*. Healthy, exceptionally long-lived persons may possibly represent a selected population with an unusually efficient immune system.[1] Moreover, thyroid autoimmunity is often associated with other autoimmune diseases, hence it was suggested that there may be a link between circulating thyroid autoantibodies and other diseases, such as atherosclerosis. However, the minor increase in coronary heart disease related to positive serum thyroid autoantibodies, reported in some epidemiological studies,[1] has not been confirmed by other reports.[1,15,16]

Other parameters, such as genetic polymorphisms in thyroid hormone pathway genes[17,18] and psychological factors,[19] have been proposed in recent years as factors influencing thyroid function tests in the elderly.

Prevalence of thyroid disease in older populations

The prevalence of thyroid disease varies widely according to age, gender and the environment. In large epidemiological studies conducted in older populations, the prevalence of hypothyroidism varies widely, from 1 to 20% of subjects, with women being more commonly affected than men and subclinical being more frequent than overt hypothyroidism. Hyperthyroidism is less common than hypothyroidism,

but it is not infrequent, occurring in 0.5–3% of all elderly patients.[1–3] In iodine-sufficient areas, hypothyroidism has been reported to occur in 4–9.5% of the general population and hyperthyroidism in 0.4–3.2%.[4,10,12,20] The most frequent disorders of thyroid function in older persons are subclinical, thanks to newly devised methods for measuring serum TSH by ultrasensitive methods and free fractions of thyroid hormones, which have improved the early detection of thyroid dysfunction in the elderly. Subclinical hypothyroidism and subclinical hyperthyroidism are 2–4-fold more common than the corresponding overt conditions and are more prevalent in the elderly and in women. Hypothyroidism is more common in iodine-sufficient areas, whereas hyperthyroidism occurs more frequently in iodine-deficient areas.[21] In the latter, toxic nodular goitre is fairly frequent.[22–25] Subclinical hyperthyroidism was present in 15% of over 75-year-old persons living in an Italian iodine-deficient area[23] and in 6.5% of over 85-year-old persons living in an iodine-sufficient area of the USA.[10] The prevalence according to gender was also different in these two studies: it was equal for both genders in the Italian survey,[23] whereas in the USA it was more frequent in women.[10] The prevalence of hypothyroidism increases with ageing in up to 20% of females and 3–16% of over 75-year-old men in iodine-sufficient areas.[12,20] The prevalence in men and women is similar in hospitalized older patients.[1]

A survey in the UK found that overt hyperthyroidism and hypothyroidism were infrequent in the community (0.3 and 0.4%, respectively). Subclinical thyroid dysfunction was present in 5% of the studied population (subclinical hyperthyroidism in 2.1% and subclinical hypothyroidism in 2.9%).[26]

The prevalence of thyroid disease is higher in hospitalized elders and in long-term facility residents, although data available in these settings come from limited number of patients.[27–32] A study conducted in four nursing homes in Cape Town reported abnormal TSH in 15.6% of residents, with only 0.5% newly diagnosed cases of overt hyperthyroidism and 1% new cases of overt hypothyroidism. Subclinical thyroid disease was present in 6% of residents.[27] In a study conducted in Spain, there were 3.7% cases of previously undiagnosed subclinical hypothyroidism, 1.65% cases of overt hypothyroidism, 0.82% cases of subclinical hyperthyroidism and 10.3% cases of autoimmune thyroid disorders.[28] Another survey in Spain reported 7.9% cases of elevated TSH at admission to a nursing home and 13% cases of NTI, suggesting that TSH measurements should be performed regularly at admission.[29] In the USA, a study in nursing homes reported overt hypothyroidism in 0.7% of men and 1.5% of women and subclinical hypothyroidism in 9.7% of men and 14.6% of women.[30] The authors suggested the screening of all institutionalized elders since those with subclinical hypothyroidism are at risk for further decline in thyroid function. Nevertheless, the progression of subclinical hypothyroidism to overt disease has been estimated in only 5% of patients.[4,5] A survey conducted in two nursing homes in Georgia, USA, aimed to determine the sensitivity of clinical determinants for hypothyroidism during withdrawal of thyroid hormone therapy. Among 129 residents, the prevalence of hypothyroidism ranged from 6.2 to 7.8%; unnecessary therapy was given to 5.4% of the studied subjects.[31] Likewise, for half of nursing home residents receiving thyroid hormone, the prescription was found unnecessary in a survey conducted in the USA.[33] A survey conducted in Eastern Europe confirmed a higher prevalence of positive antithyroid antibodies in old age that was independent of iodine supply; in the same study, iodine supply was associated with the development of autoimmune hypothyroidism in older patients.[32]

Hypothyroidism

Overt hypothyroidism is characterized by low levels of thyroid hormones and increased levels of TSH. Decreased thyroid function is not uncommon in over 60-year-old persons, it increases with age and is higher in women than men.[2,5,34–36] Hypothyroidism (overt and subclinical) is found in 5–20% of women and 3–8% of men.[34] Undiagnosed hypothyroidism can be found in as many as 25% of nursing homes residents.[31,34] Overt hypothyroidism is 5–8 times more common in women than men, with an increased prevalence (up to 5%) in persons over 60 years of age.[37] Diverse medications, such as amiodarone and lithium, may induce hypothyroidism (see Tables 98.1–98.3). The most frequent cause of hypothyroidism in old age is autoimmune thyroiditis, followed by earlier thyroid surgery or radiation therapy for previous thyrotoxicosis.[2,3,5,38]

Symptoms of hypothyroidism are often atypical, specially in the oldest elders, and lack the classic presentation seen in younger patients.[1] They include memory loss, lethargy, constipation, cold intolerance, fatigue, congestive heart failure, depression and weight gain, all of them often attributed to old age or other causes. Furthermore, lack of these symptoms does not rule out the presence of hypothyroidism, hence a high index of suspicion is needed in formulating the diagnosis. The atypical presentation is due to a more insidious onset, the concurrence of several age-associated diseases and the notion that signs and symptoms are attributable to the ageing process. An elevated serum TSH level should be confirmed and supplemented with measurements of serum thyroxine (T4) and with thyroid antibodies (Figure 98.1).

Although hypothyroidism is common in older persons, it may not necessarily be associated with adverse outcomes in the oldest individuals when detected by screening alone, as illustrated by a population-based, prospective study of 558 individuals in The Netherlands. In this study, participants were screened for hypothyroidism during the month of

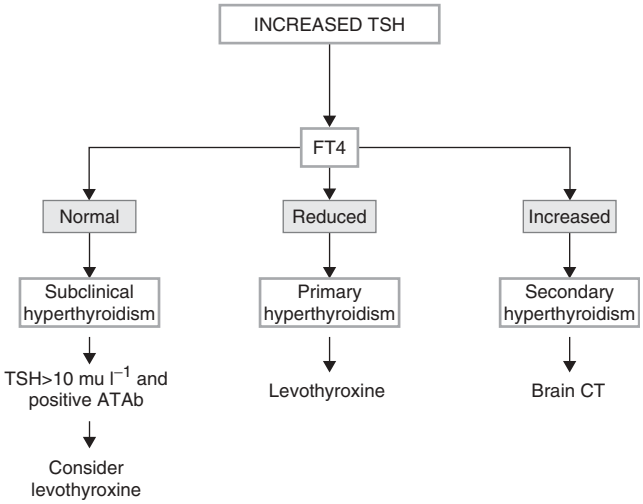

Figure 98.1 Algorithm for the diagnosis of thyroid disorders in the presence of an increased TSH. ATAb, anti-thyroid antibodies; FT3, free triiodothyronine; FT4, free thyroxine; rT3, reverse triiodothyronine; TSH, thyroid-stimulating hormone. Data from references 3, 5 and 6.

their 85th birthday and again 3 years later.[39] Annual evaluation included assessment of activities of daily living (ADLs), cognitive performance and depression scales. About 12% had hypothyroidism at baseline (7% overt and 5% subclinical). None of the patients with subclinical hypothyroidism had progressed to overt hypothyroidism when retested at age 88 years. There was no association of baseline TSH levels and cognitive function, depressive symptoms or ADLs disability. All these parameters declined over time, but the decline was not accelerated in those with subclinical or overt hypothyroidism. Conversely, increased TSH at baseline was associated with a slower decline in instrumental ADLs ability, and also with lower all-cause cardiovascular mortality despite higher serum cholesterol concentrations.[39]

In 1966, Brain *et al*. described a patient with Hashimoto's autoimmune thyroiditis under treatment with levothyroxine, who developed several episodes of cerebral disorders.[40] After this first report, the association of thyroid autoantibodies with encephalopathy (incorrectly called 'Hashimoto's encephalopathy') has been reported by a few other authors.[41,42] Nevertheless, chronic lymphocytic thyroiditis is rarely associated with serious neurological manifestations and the number of reported cases of 'Hashimoto's encephalopathy' is very small compared with the high prevalence of thyroid autoimmunity in the general population. Hence the disorder may not be caused by antithyroid antibodies or thyroid dysfunction but may represent an association of an uncommon autoimmune encephalopathy with a common autoimmune thyroid disease. Another study found a high number of perfusion defects in euthyroid patients with autoimmune thyroiditis, suggesting that cerebral vasculitis might be implicated in this condition.[43] Even if 'Hashimoto's encephalopathy' is rare, it is life-threatening and responds to therapy with corticosteroids (up to 83% of patients); for this reason, it should better be called 'corticosteroid-responsive encephalopathy'.[44] The awareness of this treatable condition is important considering the possible association of hypothyroidism symptoms and encephalopathy in an older subjects.

The decision to treat a patient with overt hypothyroidism is usually straightforward, in contrast with the decision to treat subclinical hypothyroidism (see below) that may depend on the individual presentation and on an accurate evaluation of the possible benefit to be gained with the therapy. Treatment of overt hypothyroidism in older persons should be started and monitored carefully in order to maintain TSH and FT4 within the normal range. Thyroid hormone increases myocardial oxygen consumption, which may induce angina pectoris, myocardial infarction or cardiac arrhythmias in older patients. Hence in older patients, and even more so in older patients with heart disease or multiple coronary risk factors, thyroid hormone replacement should be initiated conservatively. The initial dose of levothyroxine should be very low (12.5–50 μg per day) and should be increased slowly every 4–6 weeks, with the purpose of reaching the replacement dose after 3–4 months.[1,2,34,45] The replacement dose of levothyroxine in older people is usually lower than 1.6 μg/kg per day, which is the dose usually employed in younger patients.[46] This reduction appears to be dependent on a relative decrease in lean body mass with ageing and the physiological age-associated reduction in T4 production.[47] In older hypothyroid patients there is a narrow range between TSH suppression and substitution dose, which may be due to an increased sensitivity of the thyrotrophes to the negative feedback by T4.[1] Another good reason for giving a lower dose in the oldest patients is that two studies (in subjects >73 and >85 years of age) have shown that high TSH and/or low FT4 levels are associated with a lower mortality rate.[11,39] It is essential to examine TSH measurements carefully every 3 months and to complete hormone replacement gradually, so as to avoid over-treatment and heart and central nervous system problems, which may be seen if the replacement is accomplished too quickly. In selected patients, in particular those with heart failure or alterations of heart rhythm, a dose of levothyroxine lower than substitutive is necessary to prevent ischaemic heart symptoms. The patient and the caregiver must be warned of the possible increase in angina, dyspnea, confusion and insomnia and notify these symptoms to the prescribing physician. Over-replacement may induce osteoporosis, anxiety, muscle wasting and atrial fibrillation as adverse effects. In older patients on chronic replacement therapy with levothyroxine

sodium, estimation of serum TSH level once or twice per year is recommended, with small dosage adjustments to keep the serum TSH level within the normal range.

It is worth remembering that many older patients began taking thyroid hormone therapy when younger either for inappropriate reasons or for transient hypothyroidism, and they continue to take it without control. A study of nursing home residents reported that thyroid hormone therapy was successfully withdrawn from half of the residents studied.[33]

Subclinical hypothyroidism

The current widespread availability of greatly sensitive assays and more frequent assessment of serum TSH concentrations has lead to a more frequent finding of subclinical thyroid disorders, which are particularly frequent in older people.[4–6] The overall prevalence of subclinical hypothyroidism is 4–10% in the general population and up to 20% in women older than 60 years.[4,5,10] Progression to overt hypothyroidism is reported to vary from 3 to 20%, the risks being greater in those patients with goitre or thyroid antibodies, or both, but it is generally around 5%. Hence patients with subclinical hypothyroidism should be followed and eventually treated.[4,5,12] (Figure 98.1).

This disorder is defined as an elevated serum TSH level in the face of normal or normal-low free thyroid hormone values. The finding of a TSH measurement over 4.5 mU l^{-1} should be confirmed within 1–3 months and repeated every 6–12 months in asymptomatic patients. If the value is confirmed, the possibility of past radioiodine administration, previous thyroid surgery, the presence of thyroid enlargement and history of thyroid dysfunctions in the family should be considered. In addition, exploration of subtle clinical signs of hypothyroidism and evaluation of lipid profile are suggested. Antithyroid antibodies are useful for improving the prognosis of progression to overt hypothyroidism but they may not change the management of the patient. If during follow-up TSH increases to over 10 mU l^{-1}, the patient should be treated with levothyroxine. When TSH is between 4.5 and 10 mU l^{-1}, an *ex adjuvantibus* administration of levothyroxine may be considered in an individual basis to help improve subtle clinical symptoms (Figure 98.1). A consistent association of subclinical hypothyroidism with cardiovascular problems, increased LDL cholesterol or other cardiovascular problems present in overt hypothyroidism (e.g. hypertension, impaired diastolic relaxation) and to neuropsychiatric problems, is still a matter of debate.[4,5,48,49] For example, recent reports show an attenuated CHD-related morbidity and mortality in patients with subclinical hypothyroidism treated with levothyroxine,[48] but patients with acute ischaemic stroke and subclinical hypothyroidism show more favourable outcomes than those without subclinical hypothyroidism.[49]

There is still no consensus on the potential benefits and risks of therapy for subclinical hypothyroidism. Possible mechanisms proposed to explain the potential benefit include modifications in lipid profiles, coagulation parameters and low-grade chronic inflammation. Early clinical and autopsy studies had suggested an association between subclinical hypothyroidism and coronary heart disease (CHD), which was later confirmed by some,[48–52] but not all,[53–56] large cross-sectional and prospective studies. A cross-sectional study in Western Australia, with a follow-up of 20 years, examined the prevalence of CHD in 2108 subjects with and without subclinical thyroid dysfunction. There were 21 cardiovascular deaths observed compared with 9.5 expected and 33 CHD events observed compared with 14.7 expected among patients with subclinical hypothyroidism, which remained significant after further adjustment for standard cardiovascular risk factors.[57] There is evidence that restoration of euthyroidism with levothyroxine can improve LDL cholesterol levels in most patients with subclinical hypothyroidism,[52,58,59] but the reduction of cardiovascular events remains to be elucidated, even though a recent reanalysis of the Whickham survey reported an association between incident CHD events and CHD-related mortality with subclinical hypothyroidism over a 20 year follow-up.[48] Treatment of subclinical hypothyroidism seemed to attenuate CHD-related morbidity and mortality, which may help to explain why different longitudinal studies, which did not take into account the presence of replacement therapy, are not homogeneous. Nevertheless, a definitive answer is not yet available. The decision to treat a patient might depend on the presence of other cardiovascular risk factors, rather than on a TSH threshold. Even if levothyroxine replacement therapy is usually safe with adequate titration and monitoring of serum TSH levels, in the oldest old (>85 years of age) thyroid hormone substitution is not likely to be beneficial.[60] In effect, it may even be harmful according to two studies in subjects over 73 and over 85 years of age which showed that high TSH and/or low free T4 levels are associated with a lower mortality rate.[11,39] Perhaps the discrepant results reported in the above-mentioned studies can be explained by the fact that subclinical hypothyroidism seems to be detrimental in young to middle-aged subjects, whereas it may be harmless or perhaps beneficial at advanced age.[60] Prospective randomized studies are still needed to establish definitely whether early treatment with levothyroxine will be of any benefit in reversing CHD risk in patients with subclinical hypothyroidism.

There is still a great deal of debate concerning the possible impact of mild or subclinical thyroid disorders on cognitive function, performance and survival in older people. A prospective, observational study conducted in individuals older than 85 years in Leiden, The Netherlands, with a mean follow-up of 3.7 years reported that

neither TSH nor free T4 was associated with disability in daily life, depressive symptoms and cognitive impairment at baseline or during follow-up. Moreover, elevated TSH levels were associated with a lower mortality rate that remained significant after adjustment for baseline disability and health status, favouring no treatment for subclinical hypothyroidism.[39] Likewise, a recent study showed that well-functioning 70–79-year-old individuals with subclinical hypothyroidism do not demonstrate increased risk for mobility problems and those with mild elevations in TSH level show a slight functional advantage.[61] A cross-sectional survey, conducted in a primary care setting in England on 5865 patients older than 65 years, including 295 patients with subclinical thyroid dysfunction, reported no association of mild thyroid dysfunction with cognition, depression and anxiety, after adjustment for comorbid conditions and use of medications.[62] However, other studies have shown an association of subclinical hypothyroidism with depression in older subjects.[63,64]

Hyperthyroidism

Overt hyperthyroidism is characterized by high levels of thyroid hormones and a low TSH. The most common causes of hyperthyroidism in the elderly are Graves' disease in iodine-sufficient areas and nodular goitre (Plummer's disease or multinodular toxic goitre) and functioning follicular thyroid adenoma in iodine-deficient areas.[6,22,23,65] Transient thyrotoxicosis may occur in subacute thyroiditis and during treatment with amiodarone (particularly in iodine-deficient areas), which may represent a major therapeutic challenge.[66] Transient thyrotoxicosis during treatment with levothyroxine and interferon are self-limited and remit with drug withdrawal.

Whereas in younger patients there are multiple emblematic symptoms related to an overactive thyroid, the older patient may have few symptoms and they are frequently atypical. Patients often lack the hyperdynamic symptomatology (tremor, heat intolerance, ocular signs, nervousness or tachycardia) typical of the young hyperthyroid patient and instead have a more sedated, apathetic presentation. However, the frequency of atrial fibrillation is higher. Weight loss and cardiac symptoms frequently predominate and goitre is frequently absent, making the diagnosis less obvious than in the younger patient.[1–3] In addition, depression and mania can be manifestations of hyperthyroidism in the elderly.

Treatment of older patients with hyperthyroidism includes antithyroid drugs and radioactive iodine (^{131}I). ^{131}I is the treatment of choice, especially when concomitant cardiovascular diseases are present, while surgery may be considered if obstructive symptoms caused by large goitres are present, even if it is rarely indicated because of the high operative risk in older subjects with comorbidity.[1,3,65] Nevertheless, radioiodine may be also successfully used in large compressive goitres.[67] Treatment with beta-blockers may prevent symptoms of thyrotoxicosis following ^{131}I treatment and in general atrial fibrillation reverts to sinus rhythm within a few months after restoration of euthyroidism. Antithyroid drugs (methimazole or propylthiouracil) may be the treatment of choice for controlling hyperfunction before a definitive treatment with ^{131}I. Beta-adrenergic blockers (propranolol, metoprolol) may be used with prudence and, when needed, the dosage should be the lowest possible.[3,65] Treatment of an underactive thyroid after definitive treatment with ^{131}I is simpler than recurrence of hyperthyroidism in an older patient.

Subclinical hyperthyroidism

The finding of TSH levels below 0.45 mU l^{-1} in the presence of thyroid hormones in the normal or high borderline range is indicative of subclinical hyperthyroidism. As with hypothyroidism, the prevalence of overt hyperthyroidism is much lower than the subclinical dysfunction (3.2%, which decreases to 2% after exclusion of subjects with known thyroid disease).[4,10] In most cases, the cause is recognized: initial Graves' disease, initial nodular toxic goitre, excessive TSH suppressive therapy with levothyroxine for benign thyroid nodular disease or differentiated thyroid cancer or hormone over-replacement in patients with hypothyroidism. However, other causes of a low TSH, such as NTI, fasting and the use of drugs (e.g. glucocorticoids), should be excluded before making the diagnosis. Subclinical hyperthyroidism in older people may be associated with relevant signs and symptoms of excessive thyroid hormone action leading to an important reduction in the quality of life.[6,35,68]

Subclinical hyperthyroidism is usually associated with a higher heart rate and a higher risk of supraventricular arrhythmias, especially atrial fibrillation (three times the risk compared with controls)[69] and with an increased left ventricular mass, often associated with impaired diastolic function.[70,71]

It is becoming increasingly apparent that subclinical hyperthyroidism may decrease bone mineral mass and accelerate the development of osteoporosis and fragility fractures, particularly in postmenopausal women with a pre-existing predisposition,[35,72,73] hence patients with subclinical hyperthyroidism should be carefully evaluated. TSH measurement should be repeated and, if the low value is confirmed in a patient with atrial fibrillation or cardiovascular or other medical problems, a thyroid scintigraphy may help to consider the presence of a toxic goitre, Graves' disease or thyroiditis (in the destructive phase) (Figure 98.2).

A retrospective study investigating nursing home residents with low TSH and normal total T4 levels showed that only three out of 40 patients with subclinical

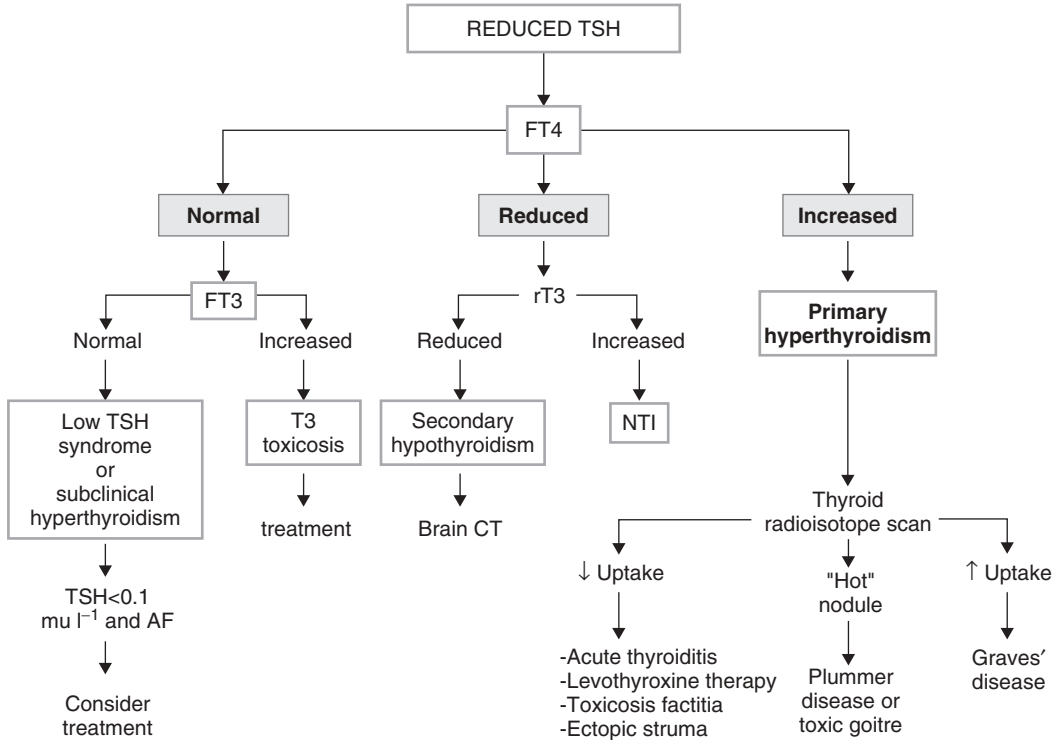

Figure 98.2 Algorithm for the diagnosis of thyroid disorders in the presence of a reduced TSH. AF, atrial fibrillation; ATAb, anti-thyroid antibodies; FT3, free triiodothyronine; FT4, free thyroxine; NTI, non-thyroidal illness; rT3, reverse triiodothyronine; TSH, thyroid-stimulating hormone. Data from references 3, 5 and 6.

hyperthyroidism became overt hyperthyroid. However, 17.5% of subjects with subclinical hyperthyroidism died during the first 4 months of follow-up compared with 7.5% in a control group, and 22.5% of subjects with subclinical hyperthyroidism had a history of or current atrial fibrillation, confirming the importance of identification of subjects at risk.[74] Regarding cognition, a recent study reported a higher risk (hazard ratio 2.26) of having cognitive dysfunction among participants with subclinical hyperthyroidism compared with those with normal thyroid function.[75]

The Cardiovascular Health Study of 3233 US community-dwelling individuals older than 65 years enrolled in 1989–1990 and reassessed through 2002 reported an incidence of subclinical hyperthyroidism of 1.5%. After exclusion of those with prevalent atrial fibrillation, persons with subclinical hyperthyroidism had a greater incidence of atrial fibrillation than those with normal thyroid function, with no differences for incident CHD, cerebrovascular disease, cardiovascular death or all-cause death.[54] Conversely, a population-based study in a cohort of 1191 individuals older than 60 years evaluated after 10 years in England and Wales revealed a significantly increased total and cardiovascular mortality in the first 5 years after first measurement in those with low TSH.[56] In fact, the association of endogenous subclinical hyperthyroidism with cardiovascular mortality is still controversial,[76] perhaps due to a lack of homogeneity among the diverse studies published on the subject, even meta-analyses giving conflicting results. Two studies with similar characteristics in terms of selection criteria and duration of follow-up but conducted in different populations (German and Japanese-Brazilian) reported opposite results.[77,78] Therefore, it remains controversial whether or not to treat middle-aged patients with low serum TSH levels until large prospective randomized controlled double-blind studies of young and old patients with subclinical hyperthyroidism and without underlying cardiac disease are available.

In view of the fact that subclinical hyperthyroidism and its related clinical manifestations are reversible, may in some cases cause significant morbidity and mortality and may be prevented by timely treatment,[35] it is important to consider the possible benefit of treatment on an individual basis. At present, most authors are in agreement regarding the treatment of elderly patients with subclinical hyperthyroidism and a clearly suppressed TSH level ($<0.1\,mU\,l^{-1}$) and follow-up for patients with TSH levels between 0.1 and $0.4\,mU\,l^{-1}$.[4,79,80] Beta-blockers have been proposed to reduce the cardiac effects of levothyroxine suppressive treatment.[35]

Another important issue is the cardiac and skeletal effects of long-term TSH suppression used to reduce thyroid cancer recurrence. According to recent guidelines from the American Thyroid Association, it is necessary to consider age, the presence of pre-existing cardiovascular and skeletal risk factors and the aggressiveness of thyroid cancer to decide the TSH target and to balance better the benefit against the potential adverse effects of long-term TSH suppression. In addition, adequate intake of calcium and vitamin D to prevent osteoporosis should be encouraged.[81]

Non-thyroidal illness (NTI)

Age-related diseases, both acute and chronic, and also malnutrition may modify thyroid tests either to mask existing thyroid dysfunction or to induce changes which simulate abnormal results by spuriously increasing or decreasing circulating concentrations of thyroid hormone and levels of pituitary TSH and transport proteins. In mild illness, a decrease in serum T3 levels can be found. However, as the severity and duration of the illness increase, both serum T3 and T4 decrease, without an elevation of TSH. The decrease in hormone levels is seen in starvation, sepsis, surgery, myocardial infarction, bypass, bone marrow transplantation and in fact probably any severe illness. This is often referred to as NTI,[82–84] which is also called 'euthyroid-sick syndrome'; however, in some sick patients it is possible that an acquired transient central hypothyroidism is present,[82,84] hence they may not be 'euthyroid', but this is still a controversial area.[84–86] Recently, evidence has accumulated that central hypothyroidism and altered peripheral metabolism of T4 and T3 combine to produce a state characterized by diminished serum and tissue supplies of thyroid hormones. The high prevalence of NTI in older populations is an important confounder in the assessment of thyroid function. For example, in a study including 403 healthy ambulatory men (aged 73–94 years), excluding subjects with systemic infectious, inflammatory and malignant disorders, 63 men met the criteria for NTI (low T3 and high rT3).[11] The subjects with NTI were older and more frequently had diseases such as hypertension, atherosclerosis, diabetes, chronic obstructive pulmonary disease, congestive heart failure and/or arthritis. Of note, high rT3 was associated with a low performance score independent of disease, probably due to the nutritional status, since caloric deprivation is known to result in an increase in serum rT3 levels.[87]

Systemic illnesses have multiple effects on thyroid hormone metabolism and on serum thyroid hormone concentrations, even in the absence of specific hypothalamic, pituitary or thyroid diseases. These changes seem to be primarily related to the severity and chronicity of illnesses,[88] rather to the specific disease states. Malnutrition and/or increased catabolism related to chronicity, which result in progressive declines in thyroid-binding protein concentrations, may play a key role in NTI. In addition, the ageing process itself is associated with decreased serum levels of T3 and TSH concentrations that are to some extent independent of NTI.[1] Despite these abnormalities, treatment of NTI patients with thyroid hormone, although controversial, appears to be of little benefit and it may even be harmful.[89] It has long been proposed that the changes in thyroid function during severe illness are protective in preventing excessive tissue catabolism.

The mechanisms proposed to mediate NTI are listed in Table 98.4.[84,90–96] These mechanisms include an induction of central hypothyroidism due to reduced hypothalamic TRH, probably signalled by a decrease in leptin caused by malnutrition and possibly a localized increase in hypothalamic T3 catalysed by altered expression of hypothalamic T3 deiodinases D2 and D3. In acute illness, a fall in T3 and T4 precedes the fall in hepatic D1, hence decreased thyroid hormones may be attributable to an acute phase response inducing a reduction in thyroid-hormone binding capacity of plasma.[84]

Measurement of serum rT3, the product of 5-monodeiodination of T4, may occasionally be helpful in distinguishing between NTI and central hypothyroidism, since rT3 concentrations are usually high in patients with NTI and low in patients with central hypothyroidism.[86,89] Thyroid hormones are low largely because of reductions in thyroid hormone-binding proteins. Not often, free T3 and free T4 are decreased because circulating substances may inhibit binding to thyroid hormone-binding proteins, such as free fatty acids or cytokines.[90] Almost all patients with subnormal but detectable TSH levels (<0.3 and $>0.05\,mU\,l^{-1}$) will be euthyroid when reassessed after recovery from the acute illness. On the other hand, most patients with undetectable serum TSH levels ($<0.01\,mU\,l^{-1}$) have hyperthyroidism.[65] Numerous drugs have important effects on thyroid function and/or on thyroid function test (Tables 98.1–98.3) and polypharmacy is very frequent in older patients, hence this non-thyroidal factor should be considered. A study evaluating 1153 determinations of T4 in nursing homes identified 22 individuals with low T4 and normal TSH, of whom 36% were treated with high-dose salicylates, 18% with phenytoin, 14% with carbamazepine and 9% with prednisone. Six of the 22 were placed on levothyroxine replacement without documentation of hypothyroidism, although in five of them, low T4 could be attributed to a medication effect.[97]

There is even greater uncertainly about hormone replacement therapy in ill patients with low serum T4 or T3 concentrations. It has been repeatedly recommended not to start replacement treatment, even if there is no factual support for that observation. Hence controlled clinical trials are needed to establish an evidenced-based recommendation. However, if there is evidence to support a diagnosis of hypothyroidism (e.g. a TSH $>20\,mU\,l^{-1}$

Table 98.4 Possible mechanism of non-thyroidal illness (NTI)[a].[84,90–96]

	Low T3	Low T4	Low TSH	Low TRH
Albumin	Reduced	–	–	–
TBPA	Reduced	–	–	–
TBG	Reduced	Reduced	–	–
TRH	Reduced	Reduced	Reduced	Reduced
Dopamine	–	–	Increased	–
Glucocorticoids	–	–	Increased	–
NEFA	Increased	–	–	–
INF	–	Increased	Increased	–
Leptin	–	Reduced	–	Reduced
IL1	Increased	Increased	Increased	–
IL6	Increased	Increased	Increased	–
TNFα	Increased	Increased	Increased	–
D2, D3	–	–	–	Increased
Competitors for TH binding	Increased	Increased	–	–

[a]D2, D3, deiodinases 2 and 3; IL, interleukin; INF, interferons; NEFA, non-esterified fatty acids; TBG, thyronine-binding globulin; TBPA, thyroxine-binding prealbumin; TH, thyroid hormone; TNF, tumour necrosis factor; TRH, thyrotropin-releasing hormone

with low free T4 and/or history, symptoms and signs of hypothyroidism), prudent administration of thyroid hormone is appropriate.[85]

Thyroid nodules and nodular goitre

Most thyroid nodules (~95%), which occur with increasing frequency in older people, are benign. Nonetheless, clinical evaluation should be considered for all thyroid nodules given a 5–13% risk of evolving into thyroid malignancy.[98] The risk of malignancy is similar for solitary nodules and multinodular goitres; urgent referral to secondary care is necessary only if the nodule is growing rapidly (over a few weeks) or associated with stridor, hoarseness or cervical lymphadenopathy.[99] Goitre is more common in women than in men.[100] The American Association of Clinical Endocrinologists (AACE) reports a prevalence of palpable thyroid nodules in 3–7% in North America; however, the prevalence increases to ~50% based on ultrasound (US) or autopsy data.[98] Generally, goitre size increases with ageing and thyroid nodularity develops, with the largest goitres observed in the oldest age groups living in iodine-deficient areas. The prevalence of diffuse and nodular goitre in young adults participating in an iodine-deficient area survey (Pescopagano study) was 30% in young adults and increased to 75% in the age group 55–65 years, with nodular goitre accounting for about one-third of the total.[23]

Fine-needle aspiration biopsy (FNAB) is the most accurate method in the evaluation of a thyroid nodule, helping to determine which patients should be referred for surgery. Its accuracy is improved by high-resolution US guidance, which can also add useful information. Nonetheless, none of the US findings are diagnostic and FNAB remains the cornerstone of thyroid cancer diagnosis.[99] Thyroid cancer in old age is generally well differentiated, but its course is frequently less predictable than in younger patients. Lymphoma of the thyroid and undifferentiated cancers occur with increasing frequency in the elderly. Multinodular goitre, usually longstanding, is frequently seen in old age and thyroid hormone suppressive therapy not only is not indicated but also may contribute to exogenous hyperthyroidism with heart and bone adverse effects.[2] The physical examination of women with goitre may be complicated by hyperkyphosis and changes in posture associated with osteoporosis; if the thyroid gland can be palpated in an older woman, it is probably enlarged. Calcification of large goitres may be associated with dyspnea, dysphagia or dysphonia and can be misdiagnosed as cancer metastases to lymphoid nodes, hence FNAB is recommended to determine the nature of calcified lesions.[101] According to AACE guidelines, thyroid US should not be performed as a screening test; however, patients with a palpable thyroid nodule should undergo US examination. Management depends mainly on the results of needle aspiration but should also take into consideration the clinical and US features. FNAB (with or without US guidance) is recommended for nodules 10 mm or larger in diameter, with one or more of the following US characteristics: irregular margins, chaotic intranodular vascular spots, a more tall than wide shape and microcalcifications.[98] US–FNAB is suggested for nodules smaller than 10 mm only if clinical information or US features are suspicious. In general, FNAB is highly accurate.

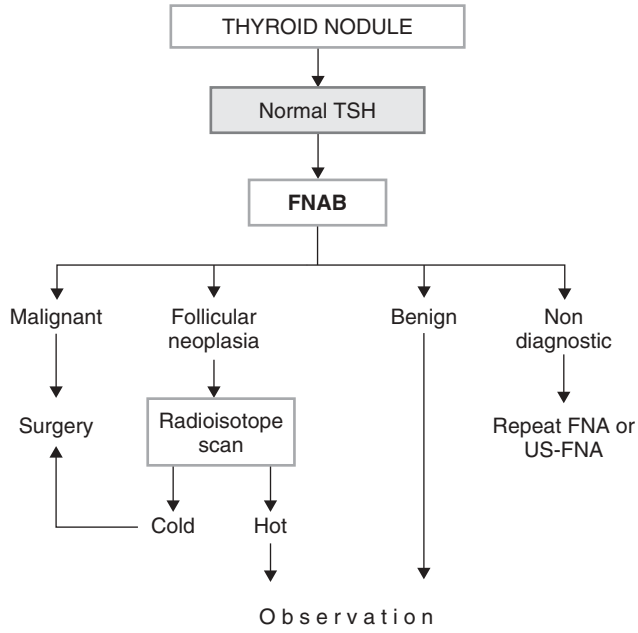

Figure 98.3 Algorithm for the diagnosis and management of thyroid nodules in the presence of normal TSH. FNAB, fine-needle aspiration biopsy; TSH, thyroid-stimulating hormone; US, ultrasound. Data from references 98–100.

However, a major limitation of FNAB is inadequate or indeterminate results, which occur in 10–25% of cases. In such cases, surgery is usually recommended for diagnosis, with the majority of these nodules proving to be benign.[98,100]

Benign thyroid nodules revealed by FNAB should undergo follow-up and malignant or suspicious nodules should be treated surgically. A thyroid radioisotope scan is useful if the TSH level is low or suppressed. Large, symptomatic goitres may be treated surgically or with radioiodine. Routine measurement of serum calcitonin is not recommended.[98] Figures 98.3 and 98.4 illustrate a suggested algorithm for the diagnosis and management of thyroid nodule.

A nodule(s) in multinodular goitre may become autonomous with ageing and progress to overt thyrotoxicosis, while large goitres may cause obstructive symptoms. When a goitre is asymptomatic, follow-up is the choice, whereas treatment is necessary in the case of toxic goitre or compressive symptoms. Suppressive levothyroxine treatment is generally not recommended in old age. ^{131}I is the first-choice treatment for thyroid autonomy and hyperthyroidism, whereas surgery is advised for large, non-toxic goitres causing significant compressive symptoms. ^{131}I therapy has been proposed in order to reduce thyroid volume in non-toxic goitres,

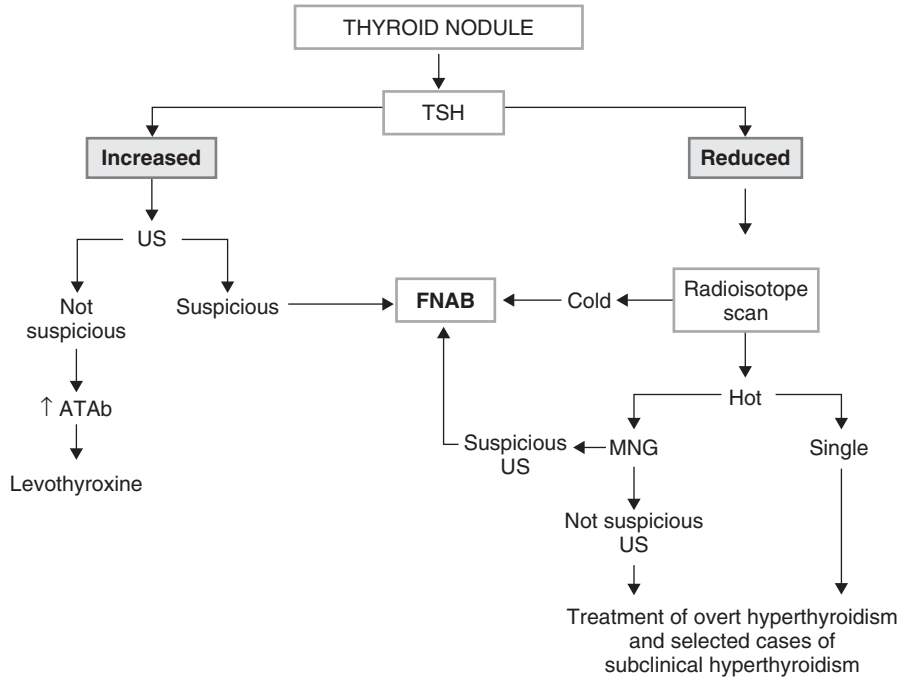

Figure 98.4 Algorithm for the diagnosis and management of thyroid nodules in the presence of an increased or reduced TSH. ATAb, anti-thyroid antibodies; FNAB, fine-needle aspiration biopsy; MNG, multinodular goitre; TSH, thyroid-stimulating hormone; US, ultrasound. Data from references 98–100.

with satisfactory results, even in the presence of structural and functional heterogeneity and large variability in ^{131}I dose. Pretreatment with recombinant TSH (rhTSH) may increase the efficacy of ^{131}I therapy.[102] However, since these strategies have been reported in relatively small studies with different thyroid size and function, definitive conclusions and recommendation cannot be drawn. Furthermore, severe acute adverse effects caused by radiation-induced thyroiditis and oesophagitis after rhTSH pretreatment have been reported, hence appropriate management protocols need to be defined.[103]

Conclusion

Ageing is associated with a number of thyroid function modifications. However, it is not simple to discern whether and to what extent these changes are an expression of the ageing process *per se* or of an age-associated thyroidal and/or non-thyroidal illness. Ageing is frequently associated with an increased prevalence of thyroid autoantibodies, which may be an expression of age-associated disease rather than a consequence of the ageing process itself. Thyroid diseases in older patients differ from those observed in younger patients in their prevalence, which is higher especially among women, and clinical expression. Their treatment often deserves special attention because of the increased risk for complications (e.g. cardiac arrhythmia, cognitive decline, bone loss). The thyroid hormone replacement dose in older people with overt hypothyroidism is usually lower than that in younger people and should be increased slowly every 4–6 weeks. Definitive treatment with ^{131}I is the treatment of choice for overt hyperthyroidism, especially when concomitant cardiovascular diseases are present, whereas surgery may be considered if important obstructive symptoms are present.

There is often significant delay and difficulty in the diagnosis of thyroid disorders in old age because clinical presentation is paucisymptomatic and attributed to normal ageing and because atypical presentations are not uncommon. Routine screening of asymptomatic, healthy adults is not recommended; however, physicians should maintain a high index of suspicion for testing thyroid function in subjects at risk. The interpretation of thyroid function tests may be complex in old individuals because of age-associated changes in thyroid function and also because of frequent alterations secondary to NTI, malnutrition and/or drugs. Subclinical abnormalities of thyroid function are more prevalent than overt disease in old populations. Subclinical hyperthyroidism appears to be a significant risk factor for cardiac arrhythmia, especially atrial fibrillation and fragility fractures in old age. The benefits of treatment of subclinical disease are not completely elucidated. Nonetheless, subclinical hypothyroidism has been linked to increased mortality in middle-aged and young elderly subjects, possibly via its atherogenic potential, but mild thyroid dysfunction appears to be devoid of unfavourable effects and possibly even be protective in the oldest-old persons. Hence the decision to treat subclinical conditions should be individualized and restricted to high-risk patients to avoid side effects of unnecessary thyroid replacement and antithyroid medications in vulnerable elderly, in whom appropriate caution and careful dose adjustments are needed. Treatment of thyroid disease deserves especial attention in the oldest patients because of the increased risk for complications and the lack of evidence-based data in this population.

Even if most of thyroid nodules in older persons are benign, clinical evaluation should be considered for timely identification of thyroid malignancy. FNAB remains the cornerstone of thyroid cancer diagnosis, and its accuracy may be improved by high-resolution US evaluation. Nonetheless, none of the US findings are fully diagnostic.

Key points

- Although thyroid disorders in older persons are frequent, they are difficult to suspect and diagnose (similar to ageing itself or other diseases and confounded by polypharmacy, malnutrition and comorbidity).
- Thyroid disorders have an important effect on quality of life, hence overt clinical disease should be identified in a timely manner and be adequately treated.
- Although no consensus regarding the wide treatment of subclinical thyroid disorders has been achieved, identification of subjects at highest risk is warranted, especially for subclinical hyperthyroidism.

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CHAPTER 99

Ovarian function and menopause

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Introduction and definitions

As life expectancy increases beyond the eighth decade worldwide, particularly in developed countries, an increasing proportion of the female population is postmenopausal. With the average age of menopause being 51 years, more than one-third of a woman's life is now spent after menopause. Here symptoms and signs of estrogen deficiency merge with issues encountered with natural aging. As the world population increases and a larger proportion of this population is made up of individuals over 50, medical care specifically directed at postmenopausal women becomes an important aspect of modern medicine.

In an attempt to define the stages of reproductive aging and its clinical and biochemical markers, the Stages of Reproductive Aging Workshop was held in 2001 to develop a useful staging system and to revise the nomenclature. This system provides useful clinical definitions of the menopausal transition, perimenopause, menopause and postmenopause as follows:

- ***Menopausal transition.*** The menopausal transition begins with variation in menstrual cycle length and an elevated serum follicle-stimulating hormone (FSH) concentration and ends with the final menstrual period (not recognized until after 12 months of amenorrhoea). Stage – 2 (early) is characterized by variable cycle length (>7 days different from normal menstrual cycle length, which is 21–35 days). Stage – 1 (late) is characterized by two or more skipped cycles and an interval of amenorrhoea of ≥60 days; women at this stage often also have hot flushes.
- ***Perimenopause.*** Perimenopause means 'around the menopause', and begins in stage – 2 of the menopausal transition and ends 12 months after the last menstrual period.
- ***Menopause.*** Menopause is defined by 12 months of amenorrhoea after the final menstrual period. It reflects complete, or near-complete, ovarian follicular depletion and absence of ovarian estrogen secretion.
- ***Postmenopause.*** Stage +1 (early) is defined as the first 5 years after the final menstrual period. It is characterized by further and complete damping of ovarian function. The majority of women in this stage have symptoms. Stage +2 (late) begins 5 years after the final menstrual period and encompasses the ageing process until death.

Epidemiology

Menopause occurs secondary to a genetically programmed loss of ovarian follicles.

Although the average age at menopause is approximately 51 years, for 5% of women it occurs after age 55 years (late menopause) and for another 5% between ages 40 and 45 years (early menopause). Menopause occurring prior to age 40 years is considered to be premature ovarian failure. Unlike the average age of menarche, which has been affected over time by trends in nutritional status and general health, the average age of menopause has not changed much over time. A number of factors are thought to play a role in determining an individual woman's age of menopause, including genetics, ethnicity, smoking and reproductive history.

- ***Genetics.*** Based on family studies, heritability for age of menopause averaged 0.87, suggesting that genetics explain up to 87% of the variance in menopausal age. Other than gene mutations that cause premature ovarian failure (explained later in this chapter), no specific genes have been discovered to date that account for this genetic influence. However, several genes are likely involved, including genes coding telomerase, which is involved in ageing.
- ***Ethnicity.*** Ethnicity and race may also affect the age of menopause. Natural menopause occurs earlier among Hispanic women and later in Japanese-American women, compared with Caucasian women.
- ***Smoking.*** The age of menopause is reduced by about 2 years in women who smoke.
- ***Reproductive history.*** There is a tendency for women who never had children or who had shorter cycle length

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during adolescence (a predictor of high basal FSH) to have earlier menopause.

Endocrinology and neuroendocrinology of menopause

Menopause is associated with a marked decline in oocyte number that is attributable to progressive atresia of the original complement of oocytes. However, the evidence for absolute oocyte depletion is limited. Residual oocytes and differentiating follicles have been identified in the ovaries of some postmenopausal women, although the follicles are frequently atretic.

Late reproductive stage

A decline in fertility begins in the third to fourth decade of life but accelerates rapidly after the age of 35 years in association with a well-documented decrease in the pool of ovarian follicles. This age-related decrease in follicle number and fertility is marked by a rise in FSH in the early follicular phase before increases in luteinizing hormone (LH) or decreases in estradiol. The presence of regular menstrual cycles and an increase in follicular-phase FSH define the late reproductive stage. In older ovulatory women, the early follicular phase peak in FSH occurs earlier with reference to the onset of menses than in their younger counterparts and the day 3 FSH value is widely used as an indicator of reproductive ageing in clinical settings.

Studies of reproductive ageing have provided important insights into the physiology of inhibin in humans and the role of the inhibins in the selective negative feedback regulation of FSH. Inhibin A and B are secreted differentially during the normal menstrual cycle (for a review, see the key references at the end of this chapter). The pattern of inhibin B secretion suggests that it is primarily secreted from small antral follicles; inhibin B increases across the luteal–follicular transition, reaching a peak in the mid-follicular phase, and is not correlated with the size of the dominant follicle. Inhibin B expression in the ovary is confined to the granulosa cells and is absent from the theca. In the quiescent ovary, inhibin B levels in serum increase in response to FSH administration, preceding secretion of estradiol and inhibin A. Secretion of inhibin B from human granulosa cells is not stimulated directly by FSH or cyclic adenosine monophosphate (AMP), however, but rather its secretion is constitutive.

Thus, the increase in inhibin B in response to endogenous or exogenous FSH is secondary to the recruitment of a cohort of follicles into the growing pool accompanied by a dramatic increase in granulosa cell number. During folliculogenesis, peak levels of inhibin A occur in the late follicular phase and inhibin A is correlated with the size of the dominant follicle in normal cycles, as is estradiol. Inhibin A is produced by granulosa cells in response to stimulation by FSH in small follicles and both LH and FSH at later stages of follicle development. Inhibin A is also secreted from the corpus luteum, its secretion paralleling that of progesterone.

The decrease in developing follicles is reflected in a parallel decrease in the serum concentration of inhibin B, which is probably the earliest easily measurable marker of follicular decline. The rise in the serum concentration of FSH in early menopause is also closely related to the fall in inhibin B; this suggests that inhibin B plays an important role in the normal control of FSH secretion. Serum concentrations of Müllerian-inhibiting substance (MIS) [also known as anti-Müllerian hormone (AMH)] may be a useful marker reflecting reproductive ageing. Low serum AMH concentrations were predictive of a poor ovarian response to exogenous gonadotropin stimulation and may mark a critical juncture in the timing of the menopausal transition.

Menopause transition

The onset of irregular cycles defines the transition from the late reproductive years to the menopausal transition. Variable cycle length is defined as cycle lengths that are more than 7 days different from an individual's normal cycle length and may therefore include cycles with both abnormally long and abnormally short intermenstrual intervals.

The menopausal transition is characterized by a dynamic period of markedly changing hypothalamic–pituitary feedback from the ageing ovary. There is a progressive decrease in menstrual cycle regularity and dramatic swings in estradiol from undetectable to levels that are several times higher than those observed in the ovulatory cycles of younger women. Levels of inhibin A and B are further decreased and FSH levels are generally much higher than during the regular cycles of the late reproductive years. FSH levels may occasionally decrease to near the normal range in association with prolonged increases in estradiol, however. The majority of longitudinal studies indicate that the menopausal transition is not a low-estrogen state but is characterized by widely fluctuating levels of estrogen that are often increased in comparison with earlier stages of reproductive life. These fluctuations in estrogen levels in particular are likely to account for many of the symptoms of the transition to menopause.

In addition to the decline in follicular number, there may be a decrease in hypothalamic–pituitary sensitivity to estrogen-positive feedback during perimenopause.

Postmenopause

Later, with the final menstrual period, levels of inhibin A and estradiol decrease dramatically and there is a further increase in FSH and LH. In particular, the loss of estradiol

feedback on LH and FSH and inhibin feedback on FSH associated with menopause results in a 15-fold increase in FSH levels and a 10-fold increase in LH levels in comparison with the early follicular phase in healthy women in whom estradiol levels are at their nadir in the menstrual cycle. The loss of ovarian function at menopause is also associated with marked changes in hypothalamic and pituitary function. There is now evidence, however, that age-related neuroendocrine changes occur that are independent of those caused by the loss of ovarian feedback on the hypothalamic and pituitary components of the reproductive axis. There is an increase in the overall amount of gonadotropin-releasing hormone (GnRH) secreted despite a decrease in GnRH pulse frequency with ageing.

In addition, following menopause, gonadotropin levels decrease progressively with age. Studies in postmenopausal women indicate that between the ages of 45–55 and 70–80 years, there is a decrease of approximately 30% in mean levels of FSH from 148.6 ± 8.4 IU l^{-1} in younger postmenopausal women to 107.0 ± 5.4 IU l^{-1} in older women. There is a similar degree of change in LH from 95.8 ± 7.3 to 60.4 ± 3.9 IU l^{-1} in younger and older postmenopausal women, respectively. Whether the decline in gonadotropin secretion with age is caused by hypothalamic or pituitary effects has been an area of active recent investigation.

Ovarian ageing and sex steroids changes

Hormonal integration of the reproductive system is dramatically affected by reproductive ageing. At the menopause, the final menstrual cycle, a dramatic decline in plasma estradiol level occurs and the postmenopausal ovary will cease to contribute to estradiol levels in blood. Instead, peripheral conversion of androstenedione into estrone becomes prominent. Only 5% of the thus formed estrone is converted to estradiol through the action of 17-hydroxysteroid dehydrogenase. The activity of this enzyme is in a reversible reaction converting estrone to estradiol and back, depending on the oxido-reductive state that prevails in the cell. Further, the amount of estrone generated and the associated conversion to estradiol continue to decline during the first year after menopause and stabilizes thereafter. The amount of estrone generated is a function of the abundance of androstenedione and age. The corpus luteum synthesizes progesterone and in the absence of ovulation only basal levels derived from the adrenal glands are detected. In postmenopausal women, administration of adrenocorticotrophic hormone (ACTH) dramatically increases whereas human chorionic gonadotrophin has no effect on progesterone levels, attesting to the negligible role of postmenopausal ovaries in progesterone production.

Dehydroepiandrosterone (DHEA) is produced in both the ovaries and the adrenal glands under the influence of LH and ACTH, respectively. DHEA sulfate (DHEAS) is exclusively produced by the adrenal glands and is converted to DHEA by steroid sulfatase. Their declining plasma levels are due to age-related reduced steroid synthesizing capacity of the zona reticularis and due to ovarian ageing. During the reproductive years, both the adrenal glands and the ovaries share equally in androstenedione production. Bilateral oophorectomy in premenopausal women results in a 50% reduction in serum androstenedione levels while postmenopausal ovaries contribute only 20% of its total circulating levels. Since the metabolic clearance of androstenedione is not affected by ovarian function or age, the 30% drop represents the effect of ovarian senescence.

In premenopausal women, 50% of circulating testosterone is derived from peripheral conversion of androstenedione, while the remaining testosterone production is shared between the ovaries and the adrenal glands. In postmenopausal women, testosterone levels decrease compared with young women, although ovarian synthesis after the menopause appears to contribute a higher proportion of circulating testosterone. This may be due to higher LH levels and their effect on ovarian stromal steroidogenesis. In a recent cross-sectional study, a different aspect of ovarian ageing was reported. The circulating levels of DHEA, androstenedione and total and free testosterone were found to be highest during the third decade of life and to decline afterwards in the remaining reproductive years. Around the age of 50 years, free and total testosterone levels decrease by about 50%. Testosterone exists in circulation as free testosterone (1–2% of the total), loosely bound to albumin (31%) and tightly bound to sex hormone binding globulin (SHBG) (66%). It is the free and albumin-bound testosterone that is available to cells. Many clinicians and clinical investigators use the ratio of total testosterone to SHBG to derive the free testosterone index.

SHBG is a protein synthesized in the liver. Estrogen stimulates its synthesis whereas all androgens suppress its hepatic synthesis. Obesity, particularly with upper abdominal distribution, also suppresses SHBG levels. In the postmenopausal period, SHBG levels decline and that may account for the higher bioavailability of testosterone. A decrease in bioavailable testosterone level may result from impaired testosterone production or from increased SHBG levels in the presence of normal testosterone production. It is therefore necessary to consider SHBG levels in the assessment of bioavailable testosterone in women.

Surgical menopause

As can be expected, the removal of both ovaries in a premenopausal woman results in an abrupt decline in estrogen to undetectable levels, a 50% reduction in androstenedione and about a 70% drop in DHEA and testosterone levels. These women experience a sudden onset of the menopausal

transition. In at least 30–50% of cases, symptoms of androgen deficiency are experienced despite 'adequate' estrogen replacement.

Specific healthcare problems in relation to the menopause

As many as 80% of women experience one or more physical or psychological symptoms of estrogen deficiency as ovarian function declines during the menopause, with almost one half of sufferers finding their symptoms distressing.

Short-term consequences of estrogen deficiency

The change in hormone levels that occurs during the climacterium, particularly the decline of estrogen, can cause acute menopausal symptoms.

Brain symptoms

Symptoms include the following:

- vasomotor symptoms (hot flushes and night sweats)
- sleep problems
- mood changes (depression and anxiety)
- sexual dysfunction
- impaired concentration and memory.

Sex steroids play pivotal neuroactive and brain region-specific roles on the central nervous system through genomic and non-genomic mechanisms. Therefore, their protective effects are multifaceted and brain region dependent. They encompass systems that range from chemical to biochemical and genomic mechanisms, protecting against a wide range of neurotoxic insults. Consequently, gonadal steroid withdrawal, during the reproductive senescence, dramatically impacts brain function, negatively affecting mood, anxiety behaviour and cognitive vitality.

The hallmark feature of declining estrogen status in the brain is the hot flush, which is more generically referred to as a vasomotor episode. Hot flushes occurs in up to 75% of women in some cultures. Hot flushes are most common in the late menopausal transition and early postmenopausal periods. They are self-limited, usually resolving without treatment within 1–5 years, although some women will continue to have hot flushes until after age 70 years. Hot flushes typically begin with a sudden sensation of heat centred on the upper chest and face that rapidly becomes generalized. The sensation of heat lasts from 2 to 4 min, is often associated with profuse perspiration and occasionally palpitations and is often followed by chills and shivering and sometimes a feeling of anxiety. Physiological studies have determined that hot flushes represent thermoregulatory dysfunction; there is inappropriate peripheral vasodilatation with increased digital and cutaneous blood flow and perspiration, resulting in rapid heat loss and a decrease in core body temperature below normal. Hot flushes usually occur several times per day, although the range may be from only one or two each day to as many as one per hour during the day and night. Hot flushes are particularly common at night. The fall in estrogen levels precipitates the vasomotor symptoms. Although the proximate cause of the flush remains elusive, the episodes result from a hypothalamic response (probably mediated by catecholamines) to the change in estrogen status. A speculative mechanism for the initiation of hot flushes is endogenous opioid peptide withdrawal. Estrogen increases central opioid peptide activity and estrogen deficiency may be associated with decreased or absent endogenous central opioid activity.

A distressing feature of hot flushes is that they are often associated with arousal from sleep. This association has been well documented by EEG studies, although, primary sleep disorders are common in this population, even in the absence of hot flushes. This disturbed sleep often leads to fatigue and irritability during the day and deficit of memory is often reported.

Psychological symptoms have been associated with the menopause, including depressed mood, anxiety, irritability, lethargy and lack of energy. Women with a longer menopausal transition and/or with more intense climacteric symptoms, surgical menopause, a history of depression, menstrual cycle-related and postpartum mood changes (premenstrual syndrome, postpartum depression), thyroid disease and unfavourable socio-environmental conditions are at greater risk of developing depression and mood disorder. Observational studies have demonstrated that, in women with a history of depression, the menopausal transition is accompanied by a significant risk of relapse.

The menopausal transition impacts a women's sexual life. Low libido is the main cause of female sexual dysfunction after the menopause. Estrogen deficiency leads to a decrease in blood flow to the vagina and vulva, which also causes decreased vaginal lubrication. Vaginal atrophy frequently determines dyspareunia. From a sexological point of view, dyspareunia in a postmenopausal patient must be treated in a timely fashion to avoid triggering a vicious circle by which dyspareunia leads to sexual dissatisfaction and therefore a further decrease in libido.

Urogenital symptoms

Vaginal dryness

The epithelial lining of the vagina and urethra are very sensitive to estrogen, and estrogen deficiency leads to thinning of the vaginal epithelium. This results in vaginal atrophy (atrophic vaginitis), causing symptoms of vaginal dryness and itching. The prevalence of vaginal dryness in one longitudinal study was 3, 4, 21 and 47% of women in the reproductive, early menopausal transition, late menopausal transition and 3 years postmenopausal stages, respectively. On examination, the vagina typically appears pale, with

lack of the normal rugae, and often has visible blood vessels or petechial haemorrhages. Vaginal pH, which is usually <4.5 in the reproductive years, increases to the 6.0–7.5 range in postmenopausal women not taking estrogen. The increase in pH and vaginal atrophy may lead to impaired protection against vaginal and urinary tract infection.

Other urinary symptoms

Low estrogen production after the menopause results in atrophy of the superficial and intermediate layers of the urethral epithelium with subsequent atrophic urethritis, diminished urethral mucosal seal, loss of compliance and irritation; these changes predispose to both stress and urge urinary incontinence.

Recurrent urinary tract infections

These are also a problem for many postmenopausal women. In addition to epithelial atrophy, estrogen deficiency can increase vaginal pH and alter the vaginal flora, changes which may predispose to urinary tract infection.

Long-term consequences of estrogen deficiency

There are a number of long-term effects of estrogen, including osteoporosis, cardiovascular disease, cognitive impairment and dementia.

Osteoporosis is a common disease that is characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fracture. Osteoporosis occurs most commonly in postmenopausal women. Estrogen deficiency has been well established as a cause of bone loss. This loss can be noted for the first time when menstrual cycles become irregular in the perimenopause. From 1.5 years before to 1.5 years after the menopause, spine bone mineral density has been shown to decrease by 2.5% per year, compared with a premenopausal loss rate of 0.13% per year. Loss of trabecular bone (spine) is greater with estrogen deficiency than is loss of cortical bone. Postmenopausal bone loss leading to osteoporosis is a substantial healthcare problem. In white women, 35% of all postmenopausal women have been estimated to have osteoporosis based on bone mineral density. Further, the lifetime fracture risk for these women is 40%. The morbidity rate and economic burden of osteoporosis are well documented. Interestingly, there are data to suggest that up to 19% of white men also have osteoporosis. Bone mass is substantially affected by sex steroids through classic mechanisms to be described later in this chapter. Attainment of peak bone mass in the late second decade is key to ensuring that the subsequent loss of bone mass with ageing and estrogen deficiency does not lead to early osteoporosis. Estrogens suppress bone turnover and maintain a certain rate of bone formation. Bone is remodelled in functional units, called bone multicentre units (BMUs), where resorption and formation should be in balance. Multiple sites of bone go through this turnover process over time. Estrogen decreases osteoclasts by increasing apoptosis and thus reduces their lifespan. The effect on the osteoblast is less consistent, but E_2 antagonizes glucocorticoid-induced osteoblast apoptosis. Estrogen deficiency increases the activities of remodelling units, prolongs resorption and shortens the phase of bone formation. The molecular mechanisms of estrogen action on bone involve the inhibition of production of proinflammatory cytokines including interleukin 1, interleukin 6, tumour necrosis factor-α (TGF-α), colony-stimulating factor-1, macrophage colony-stimulating factor and prostaglandin E_2, which lead to increased resorption. Estradiol also upregulates TGF-β in bone, which inhibits bone resorption. Receptor activation of NF-κB ligand (RANKL) is responsible for osteoclast differentiation and action.

Ageing women undergo two phases of bone loss, whereas ageing men undergo only one. In women, the menopause initiates an accelerated phase of predominantly cancellous bone loss that declines rapidly over 4–8 years to become asymptotic with a subsequent slow phase that continues indefinitely. The accelerated phase results from the loss of the direct restraining effects of estrogen on bone turnover, an action mediated by estrogen receptors (ERs) in both osteoblasts and osteoclasts. In the ensuing slow phase, the rate of cancellous bone loss is reduced, but the rate of cortical bone loss is unchanged or increased. This phase is mediated largely by secondary hyperparathyroidism that results from the loss of estrogen actions on extraskeletal calcium metabolism.

Osteoporosis has no clinical manifestations until there is a fracture. *Vertebral fracture* is the most common clinical manifestation of osteoporosis. Most of these fractures (about two-thirds) are asymptomatic; they are diagnosed as an incidental finding on chest or abdominal x-ray. *Hip fractures* are relatively common in osteoporosis, affecting 15% of women and 4% of men by 80 years of age. *Distal radius fractures (Colles fractures)* are more common in women shortly after menopause, whereas the risk of hip fracture rises exponentially with age.

Cardiovascular diseases

The clinical phenomenon that premenopausal women experience lower rates of heart disease than men because of the presence of estrogen has been recognized for many years and initially formed part of the rationale for using hormone therapy (HT) in postmenopausal women.

The possible reasons for the increase in cardiovascular disease in postmenopausal women are the accelerated rise in total cholesterol in postmenopausal women [especially in levels of low-density lipoprotein cholesterol

(LDL-C)], changes of weight, blood pressure and blood glucose with ageing and menopausal status.

The abrupt fall in circulating estrogen levels might independently contribute to the rise in blood pressure, through partly unknown mechanisms, such as a direct effect on the arterial wall and the activation of the renin–angiotensin system and of the sympathetic nervous system. Postmenopausal hypertension fosters the development of left ventricular hypertrophy and is the main factor contributing to coronary artery disease, chronic heart failure and stroke in older women.

Premature menopause and bilateral oophorectomy in young women are associated with an increased incidence of cardiovascular disease, myocardial infarction and overall mortality. Observational studies suggest an interval of 5–10 years between loss of ovarian function and the increased risk of cardiovascular disease.

However, the cellular basis for the beneficial effects of estrogen on the cardiovascular system has been elucidated only in more recent times. Experimental studies in animal models of cardiovascular disease have demonstrated that the beneficial effects of estrogen are mediated via a number of mechanisms and involve a range of cell types, including endothelial, smooth muscle and cardiac muscle cells. At this level, estrogen triggers rapid vasodilatation, exerts anti-inflammatory effects, regulates vascular cell growth and migration and confers protection to cardiomyocytes. These so-called 'extranuclear actions' do not require gene expression or protein synthesis and are independent of the nuclear localization of ERs. Indeed, some of these actions are elicited by ERs residing at or near the plasma membrane. Through complex interactions with membrane-associated signalling molecules, such as ion channels, G proteins and the tyrosine kinase c-Src, liganded extranuclear ERs lead to the activation of downstream cascades such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-OH kinase (PI3K). These cascades are responsible for important cardiovascular actions of estrogen, for instance, the activation of nitric oxide synthesis or the remodelling of the endothelial actin cytoskeleton. Moreover, these cascades play crucial roles in regulating the expression of target proteins implicated in cell proliferation, apoptosis, differentiation, movement and homeostasis.

Cognitive impairment and dementia

The detection of early neural markers of brain ageing and cognitive dysfunction is one of the main challenges for the climacterium and the initial postmenopausal period; thus, the degree of cognitive vitality during the ageing process could also depend on early clinical interventions.

The evidence that estrogen has several neuroprotective effects brings new meaning to the potential impact of the prolonged postmenopausal hypoestrogenic state on learning and memory, and also to the possible increase of vulnerability in brain injury and neurodegenerative diseases in ageing women.

Results from the Mayo Clinic Cohort Study of Oophorectomy and Aging provide the level of the long-term influence that sex steroid deprivation has on cognitive vitality. In particular, women who underwent either unilateral or bilateral oophorectomy reported an increased risk of cognitive impairment or dementia compared with others with natural menopause [adjusted hazard ratio (HR), 1.46; 95% confidence interval (CI), 1.13–1.90]. In another study, the risk of Parkinson's disease was higher in women who underwent either unilateral or bilateral oophorectomy (adjusted HR, 1.68; 95% CI, 1.06–2.67). In both studies, a younger age at menopause was associated with increased risk of neurological impairment (i.e. the linear trend was significant). In this regard, significant linear trends of increasing risk for either outcome with younger age at oophorectomy were also observed.

As a conclusion, estrogen deficiency can be defined as the initial step in a chain of causality which determines the increased risk of cognitive impairment or dementia. In support of a neuroprotective effect of estrogen, women who underwent bilateral oophorectomy before age 49 years, but were given estrogen treatment until at least age 50 years, reported no increased risk.

Epidemiological surveys, prospectively monitoring women as they progress through the menopause transition, have suggested that self-reports of decreased concentration and poor memory are frequent accompaniments of this phase of life in addition to the postmenopausal period. In the Study of Women's Health Across the Nation (SWAN), more than 40% of perimenopausal and postmenopausal women endorsed forgetfulness on a symptom inventory compared with 31% of premenopausal women. In the Seattle Midlife Women's Health Study, ~62% of midlife women reported an undesirable change in memory.

In addition, the presence of objective hot flushes is a negative predictor of verbal memory in midlife women with moderate to severe vasomotor symptoms. This relationship appears to be primarily due to night- rather than daytime hot flushes, thus supporting the concept that hot flushes and sleep disturbances are a sign of brain vulnerability to sex steroid withdrawal, with a negative impact of cognition. Hypothalamic and hypothalamic–pituitary–gonadal (HPG) axis senescence induces vasomotor symptoms and hypogonadism that could trigger menopause-related mental decline in other brain areas, before deficits in learning and cognition start to become evident.

Hormone therapy in postmenopausal women

Much confusion has arisen among healthcare providers, the lay public and the media when general concepts of risk of hormone therapy in postmenopausal women are discussed. Understanding the benefits/risks of HT is critical to clinical decision-making around the menopause and beyond.

Hormone replacement therapy after the Women's Health Initiative (WHI)

After the publication of the randomized WHI trial in July 2002, the convictions regarding hormone replacement therapy (HRT) and menopause, which had been acquired over many years, started to waver. Beforehand, the majority of the preclinical and observational studies had demonstrated that HRT reduced the risk of coronary heart disease (CHD) and, possibly, decreased the risk or delayed the onset of cognitive deficits and senile dementia. The WHI results did not confirm these data. The disparity between these findings clearly lies in the selection of subjects and timing of HRT in relation to chronological age and menopausal age.

In the observational studies, replacement hormones had been prescribed to mostly symptomatic women during the menopausal transition, who generally were younger than 55 years upon initiation of the therapy. In contrast, in the WHI trial, HRT was started after age 55 years in 89% of subjects, often after a long period from the last menstruation and in the absence of menopausal symptoms. In the observational studies, a window of opportunity, by which early hormone replacement in younger symptomatic women is protective against the endocrine–metabolic effects of hypoestrogenism, was observed. This is in accordance with the physiopathology of age-related degenerative processes, such as atherosclerosis and neuronal degeneration, which develop over many years. Instead, in the WHI trial, treatment was begun in older women for whom a late hormonal replacement could not prevent the already present cardiovascular degenerative changes.

An early start on HRT, in terms of both age and years since menopause, may represent a determining factor to induce positive effects (CHD prevention and Alzheimer risk reduction) and to limit adverse events (venous thrombosis, stroke).

Pretreatment evaluation

HRT should not be recommended without a specific indication. Before prescribing HRT, a complete medical history of the patient should be taken and a thorough physical examination performed. A mammography should be carried out within 12 months prior to HRT initiation and should be repeated during treatment according to normal screening programmes. Other diagnostic examinations, such as bone densitometry, pelvic ultrasound and blood tests, should be recommended according to the characteristics of each subject. Menopausal women should be encouraged to follow the cancer screening programmes suggested for each age range.

Indications for hormone therapy and effects on various organ systems

Menopausal symptoms

The treatment of vasomotor symptoms is the primary indication for HRT. Replacement hormones are indeed the most efficient therapy for the treatment of symptoms due to estrogen deficiency (hot flushes, sweats, urogenital atrophy symptoms). Various preparations with equal pharmacological potency have comparable effects on hot flushes. Other menopause-related symptoms such as musculoskeletal pain, changes in mood, sleep disorders and libido reduction also benefit from HRT. Low dosages are efficient in resolving vasomotor symptoms in almost all symptomatic women. It is therefore appropriate to begin hormonal therapy at low dosages and increase them after some weeks if symptoms persist.

HRT improves quality of life in postmenopausal women, especially if symptoms are associated with estrogen deficiency.

Quality of life and sexuality must be taken into account in order to have a better view of the patient and treat her appropriately. An early individualized hormonal treatment (eventually associated with androgens where necessary) may prevent or reduce sexual disturbances, improving quality of life. HRT and vaginal estrogen therapy both reduce symptoms related to urogenital atrophy (vaginal dryness, vaginitis, dyspareunia). Estrogen therapy improves irritative bladder symptoms and urinary urgency. HRT is not indicated for the treatment and prevention of stress urinary incontinence. Hormonal (estrogen) vaginal therapy is the first choice if the only indication is urogenital atrophy.

Menopausal depression

HRT may be indicated to treat first-time mild to moderate depression, particularly if it is associated with hot flushes. The treatment of severe or recurring depression should always be instituted with antidepressive drugs or psychotherapy. HRT is not efficient and, therefore, is not indicated to treat postmenopausal major depression. According to some studies, HRT may enhance the effects of antidepressive drugs. Hence HRT is not contraindicated and can be added to antidepressive therapy, especially when climacteric symptoms are present.

Postmenopausal osteoporosis

HRT reduces the risk of osteoporosis, improves bone mineral density and restores normal bone turnover. Women who take HRT have better posture and a lower tendency to fall, with an important impact on fracture incidence. Moreover, HRT determines a lower fracture risk at all skeletal sites examined in the relative studies. In particular, the WHI trial subjects receiving active treatment showed a lower incidence of all fractures with respect to the placebo group: 8.6% in women treated with HRT versus 11.25% in the placebo group (HR, 0.76; 95% CI, 0.69–0.83). Total femoral bone mineral density increased by 3.7% after 3 years of estrogen–progestin therapy versus 0.14% recorded in the placebo group ($p > 0.01$). The WHI trial confirmed the importance of an adequate concomitant calcium supplementation to prevent fractures. Low-dose hormonal therapy associated with adequate calcium supplementation adds superimposable effects to the standard dose therapy on bone mineral density and metabolism. HRT initiation after the age of 60 years is not recommended at standard doses for the sole prevention of fractures. HRT continuation after age 60 years can be taken into consideration for osteoporosis prevention only if the route of administration and the dose are adequate and the risk/benefit ratio is comparable to those with other therapies. Finally, HRT seems to be protective against osteoarthritis, the incidence of which increases after the menopause.

Metabolic syndrome

Treatment of metabolic syndrome is mostly preventive and aimed at correcting lifestyle habits, controlling blood pressure and blood glucose levels. HRT prevents the increase in body weight and android fat distribution occurring at menopause. HRT may reduce the risk of metabolic syndrome and, if started early in menopause, it may diminish the risk of cardiovascular disease.

Diabetes mellitus

Observational and randomized studies have demonstrated that HRT reduces the risk of developing diabetes mellitus. The WHI trial confirmed this [HR, 0.79; 95% CI, 0.67–0.93 in the HRT group; HR, 0.88; 95% CI, 0.77–1.01 in the estrogen replacement therapy (ERT) group].

Arterial hypertension

The management of hypertension after the menopause requires modifications in lifestyle and antihypertensive therapy. No particular class of antihypertensive drugs is indicated for menopausal hypertension. HRT is not contraindicated in postmenopausal hypertensive women provided that the blood pressure is strictly controlled with treatment.

Coronary heart disease

The cardiovascular system is profoundly influenced by sex steroids. Estrogen, progesterone and androgen receptors are present in all of the cardiovascular system. As emphasized above, the WHI trial did not confirm the reduction in CHD reported in earlier studies. The discrepancy between these findings may be due to patient selection and timing of HRT relative to chronological and menopausal age. This view is supported by a review of the WHI data regarding the effects of HRT versus placebo in younger women (within 10 years from menopause), which evidenced a reduction in CHD [relative risk (RR) 0.76; 95% CI, 0.50–1.16) similar to that reported in observational studies. The potential role of HRT in primary prevention of CHD remains hypothetical and is supported by preclinical and observational studies and *post hoc* analyses of randomized studies.

Venous thromboembolism (VTE)

Both observational and randomized studies have demonstrated a significant risk increase (RR, 2–3) of VTE in postmenopausal women treated with HRT with respect to non-treated women. The risk seems to be correlated with the dosage, is evident in the first 2 years of treatment and tends to diminish with time. Moreover, it is greater in women aged over 60 years. The WHI results showed that the risk of VTE is age dependent. In the 50–59 year age group, an increase of 11 cases per 10 000 HRT-treated women and two cases per 10 000 ERT-treated women was recorded.

Stroke

HRT tends to increase the risk of stroke in postmenopausal women, but the data are not completely concordant. In the WHI trial, 8–12 additional cases of stroke per 10 000 women treated with HRT or ERT were recorded globally per year. However, in women aged between 50 and 59 years, within 5 years from menopause, the risk of stroke associated with HRT/ERT was lower and non-significant (1–3 additional cases per 10 000 women per year). Therefore, in the WHI trial, the younger women (aged 50–59 years) experienced a non-significant increase in stroke events with, in contrast, a significantly lower total mortality. However, HRT should not be used in patients with a high risk for stroke.

Cognitive decline and dementia

Many observational studies support the role of estrogens in preventing cognitive decline and reducing the risk of dementia.

Substantial biological evidence supports the importance of estrogen to cognitive function. ERs have been identified throughout the brain and appear particularly concentrated in the basal forebrain and cortex. The basal forebrain is of special interest since it is the major source of cholinergic innervation to the hippocampus. The cholinergic system

is a neurotransmitter system important for regulation of memory and learning, and the hippocampus is the primary region of the brain mediating cognitive function. In experiments using animal models and cell lines, several mechanisms have been identified whereby estrogen may influence cognitive function:

- The cholinergic system is enhanced by estrogen. As an example, estrogen increases the synthesis of acetylcholine (the chemical that cholinergic neurons use to communicate with other nerve cells) by stimulating choline acetyltransferase activity and raises the concentration of hypothalamic nicotinic acetylcholine receptors.
- The glutamate system, a second neurotransmitter system involved in learning and memory, is also influenced by estrogen. Estrogen increases the expression of proteins from the NMDA (*N*-methyl D-aspartate) receptor, which is involved in glutamate activation and enhances long-term potentiation (the process by which we learn new things) in conditions that favour activation of NMDA receptors.
- Estrogen stimulates neurons and their ability to communicate with each other and may contribute to regulation of genes that influence neuron survival, differentiation, regeneration and plasticity.
- Estrogen may protect nerve cells from excitotoxins and may act as an antioxidant to shield nerve cells from free radical damage.
- Amyloid plaques are one of the pathological hallmarks of Alzheimer's disease and estrogen may be important in preventing amyloid deposition.

The ancillary study of the WHI on cognitive functions (WHIMS) did not show any positive effects related to HRT use. The WHIMS results are probably associated with vascular events, even at the subclinical level, in this population of advanced age. HRT initiation after age 65 years at standard dosages is not recommended for the prevention of senile dementia and cognitive decline. Although observational and preclinical studies have shown that estrogens have beneficial effects on the central nervous system and cognitive functions if treatment is begun early, before age 65 years, particularly in surgical menopausal women or if menopausal symptoms are present, available data are not sufficient to indicate or contraindicate HRT for the prevention of dementia.

Breast cancer

The risk of breast cancer represents the main impediment for HRT use. The risk of breast cancer is very fear-provoking, although the risk of dying from it is much lower than for other diseases such as lung cancer in female smokers or CHD. The lifetime risk of a woman developing breast cancer is one in eight. The slight increase in breast cancer incidence during HRT (from 30 to 36–38 cases per 10 000 women per year) has been known since the 1990s. The WHI trial confirmed this finding for long-term therapy. The risk increase for prolonged therapy (over 5 years) is smaller than for other risk factors, such as age at menarche or at first pregnancy or positive family history. The risk of breast cancer due to HRT is similar to that conferred by obesity and is not additive. In fact, HRT does not increase the risk of breast cancer in women with body mass index 42.5 $kg\,m^{-2}$, who already carry a higher risk than women with normal body weight. The risk of breast cancer tends to increase in women who take HRT for over 5 years. There is an absolute increase of six cases of breast cancer per 10 000 women per year in those treated with HRT for over 5 years with respect to the baseline incidence in non-users of 30 cases per 10 000 women per year.

The risk returns to baseline values after discontinuation of treatment. The WHI trial showed that, in hysterectomized women, ERT for over 7 years does not increase the incidence of breast cancer; on the contrary, eight fewer cases were reported per 10 000 women per year. Observational data from the Nurses Health Study have demonstrated that ERT is associated with an increase in breast cancer only after 15–20 years of treatment. Other European studies have shown that shorter periods of ERT can be associated with an increase in breast cancer. It is therefore reasonable to conclude that not all kinds of HRT determine the same modifications in breast cancer risk. It seems clear, from all the studies, that the addition of a progestin increases the risk of breast cancer with respect to the use of estrogens only or estrogens plus natural progesterone. Some data in the literature suggest that natural progesterone is associated with a lower risk of breast cancer than androgenic progestins. Breast cancer mortality is not increased in women treated with HRT. Recent data confirm that women surgically treated for breast cancer while using HRT have better survival and greater disease-free survival. HRT may cause an increase in mammographic density and this may alter the correct interpretation of the mammogram. In patients with a difficult mammographic interpretation due to an HRT-related increase in density, it is reasonable to interrupt the treatment and repeat a mammography after 30 days. Effecting HRT does not modify the optimal screening programme proposed by international scientific societies, which provides that an annual mammogram be performed.

Genital tumours

The risk of endometrial cancer increases with ERT. This risk increase has been annulled with the administration of HRT thanks to the addition of a progestin for at least 12 days per month. Endometrial cancers diagnosed during HRT are less aggressive. There is no proof compelling endometrial surveillance in patients under HRT without abnormal uterine bleeding. Cervical cancer, like adenocarcinoma of the vulva or vagina, is not influenced by sex steroids. The incidence of ovarian cancer is low. It is known that oral contraceptives reduce the risk of ovarian epithelial cancer but the

impact of HRT is not clear. Although some evidence showed an increased risk, the WHI trial did not report any significant variation in ovarian cancer risk in HRT-treated women.

Progestin use

The use of a progestin, both continuously and sequentially, is necessary to contrast the endometrial effects of estrogens, which, if administered alone, would induce hyperplasia and cancer. If these recommendations are not followed, careful endometrial surveillance is advisable. Progestins are not usually needed in hysterectomized women nor are they indicated with a vaginal administration of low-dose estrogens. Different progestins have similar endometrial effects but exert different metabolic effects according to dosage, route of administration and combination with the estrogen preparation. Therefore, it is not correct to consider all progestins alike, and it is appropriate to keep in mind the different pharmacological properties.

Considerations

Several recent guidelines have endorsed the use of HT for control of symptoms (International Menopause Society, North American Menopause Society). These guidelines underline the relative safety in symptomatic women and that lower doses should be used with individualization regarding the dose and the type of hormones, the route of administration and the length of treatment.

The risk/benefit ratio must be evaluated according to the individual characteristics of each woman (age, medical history, clinical characteristics, type of menopause, years since menopause, prevalent symptoms) that can affect the absolute risk of osteoporosis, breast cancer, CHD, stroke, diabetes and VTE. Acceptance of HRT depends on the woman's perception and correct counselling. It seems appropriate to emphasize that the incidence of any disease depends on chronological age and menopausal age. Hypoestrogenism is an important risk factor for cardiovascular disease and osteoporosis. HRT has the best risk/benefit ratio in perimenopausal women, who are younger and symptomatic and who do not manifest the endocrine–metabolic disorders that lead to degenerative diseases. In contrast, the presence of clinically manifest or subclinical chronic degenerative diseases in women over the age of 65–70 years makes systemic HRT initiation at standard doses irrational and unacceptable considering the potential associated risks.

Indications for hormone replacement therapy/estrogen replacement therapy

Indications for HRT/ERT are:

- vasomotor symptoms
- atrophy-related urogenital symptoms
- prevention of osteoporosis and related fractures.

Ascertained benefits of hormone replacement therapy/estrogen replacement therapy

Benefits of HRT/ERT are:

- prevention of atrophic involution of
  - –epithelia
  - –skin
  - –connective tissue
- intervertebral discs
- improvement of mood changes
- improvement of low libido
- improvement of sleep disturbances
- reduction of colorectal cancer risk
- improvement of musculoskeletal pain
- improvement of stress urinary incontinence.

Potential benefits of hormone replacement therapy/estrogen replacement therapy

Potential benefits of HRT/ERT are:

- improvement of many aspects of metabolic syndrome
- diabetes risk reduction
- risk reduction of Alzheimer's dementia if HRT started at menopause
- risk reduction of CHD if HRT started at menopause.

Absolute contraindications for hormone replacement therapy/estrogen replacement therapy

Absolute contraindications of HRT/ERT are:

- undiagnosed vaginal bleeding
- history of breast or endometrial cancer
- thromboembolic disorders or history of recurrent VTE
- active or chronic liver disease
- CHD
- porphyria cutanea tarda
- refusal of informed consent on behalf of the patient.

Androgen therapy in postmenopausal women

Decreases in sex hormone levels with menopause may bring about a number of consequences for women's general health and sexual wellbeing, especially when levels decline suddenly and prematurely, as in surgical menopause. In addition to the well-established role of estrogens in preserving the biological basis of sexual response, there is emerging evidence that androgens are significant independent determinants affecting sexual desire, activity and satisfaction, and also mood, energy and other components of women's health. Hypoactive sexual desire disorder (HSDD), a persistent absence of sexual fantasies or thoughts and/or desire for and receptivity to sexual activity that causes personal distress, is experienced by some postmenopausal women. Even though conventional hormone therapy with estrogens or estrogens and progestogens may be effective for vaginal atrophy, increasing vaginal lubrication and reducing

dyspareunia, it has not been shown to increase sexual desire or activity consistently and many women with sexual dysfunction remain unresponsive. Several recent, large, phase 3 studies have shown that transdermal testosterone in addition to conventional hormone therapy can be helpful in menopausal women presenting with HSDD. After 24 weeks of treatment in these studies, testosterone-treated women experienced significantly greater increases in satisfying sexual activity and sexual desire and greater decreases in distress than placebo-treated women. Accurate clinical assessment and individualized management of sexual symptoms are fundamentally important for all menopausal women with HSDD or other sexual problems.

In addition to testosterone, the marked age-related decline in serum DHEA and DHEAS has suggested that a deficiency of these steroids may be causally related to the development of a series of diseases which are generally associated with ageing. Postulated consequences of low DHEA include insulin resistance, obesity, cardiovascular disease, cancer, reduction of the immune defence and psychosocial problems such as depression and a general deterioration in the sensation of wellbeing and cognitive function. As a consequence, DHEA replacement (oral 25–50 mg per day) may be an attractive treatment opportunity and there are data that suggest that the use of oral DHEA in healthy postmenopausal women might improve condition evidenced with the ageing process, such as reduced sexual function and reduced wellbeing.

Androgen replacement therapy should be a primary choice especially in younger women with either premature ovarian or surgically induced menopause, suffering of loss of wellbeing, fatigue and loss of libido, that is not modified by estrogenic therapy. Among androgens, Δ^5-androgens such as DHEA and DHEAS, could be considered as an alternative choice to treat the androgen deficiency syndrome and/or symptomatic postmenopausal women.

Conclusion

Each phase of a woman's life is associated with specific issues related both to her reproductive health and to her general health. This is true for women globally and is specially relevant today as the majority of women (in developed countries) live for 20–30 years after the menopause.

Menopause is a clearly recognizable biological event, with a variety of potential health problems that can affect the quality and sometimes the duration of life. Deprivation of sex steroids at menopause can be defined as the initial step in a chain of causality, which determines the increased risk of several pathological conditions during the ageing process, years before their clinical manifestation.

On these bases, there is significant clinical interest in the potential long-term health effects of menopausal HT and the impact of treatment on women's health is debated.

It is becoming clear that the relative risks and benefits of treatment vary depending on a variety of factors, including age at initiation of HT, duration of therapy and the particular combination of hormones used in combined preparations. Thus, individualization of therapy is mandatory.

Changes attributed to the menopause need to be distinguished from those related to chronological ageing and HT represents an opportunity to be favourably considered in women's care, especially in the early postmenopausal period.

Key points

- The average age of menopause is 51 years.
- Estrogen deficiency has both short- and long- term consequences.
- HRT treatment requires a specific indication.
- Early HRT reduces cardiovascular disease.
- The Women's Health Initiative trial does not support the use of HRT after the age of 60 years.
- Testosterone can be used to treat hypoactive sexual desire disorder.

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CHAPTER 100

Testicular function

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Introduction

The percentage of the population in the older age group is increasing. With ageing, a significant percentage of men have a gradual and moderate decrease in testicular function. This decrease in either of the two major functions of the testes, sperm production and testosterone production, is known as hypogonadism. Hypogonadism in a male can result from disease of the testes (primary hypogonadism) or disease of the pituitary or hypothalamus (secondary hypogonadism). The main consequence is a decrease in the serum concentrations of testosterone known as late-onset hypogonadism (LOH), which is a clinical and biochemical syndrome. Testosterone deficiency is a common disorder in older men but it is underdiagnosed and often untreated. It has been estimated that only 5–35% of hypogonadal males actually receive treatment for their condition. The prevalence of hypogonadism was 3.1–7.0% in men aged 30–69 years and 18.4% in men over 70 years of age.[1] The most easily recognized clinical signs of relative androgen deficiency in older men are a decrease in muscle mass and strength, a decrease in bone mass and osteoporosis and an increase in central body fat. None of these symptoms are specific to the low androgen state but may raise suspicion of testosterone deficiency. In addition, symptoms such as a decrease in libido and sexual desire, forgetfulness, loss of memory, difficulty in concentration, insomnia and a decreased sense of wellbeing are more difficult to measure and differentiate from hormone-independent ageing. Clinicians tend to overlook it and the complaints of androgen-deficient men are merely considered part of ageing. This condition may result in significant detriment to quality of life and adversely affect the function of multiple organ systems. This LOH is important since it features many potentially serious consequences that can be readily avoided or treated. In men, endogenous testosterone concentrations are inversely related to mortality. However, this association could not be confirmed in the Massachusetts Male Aging Study (MMAS)[2] or the New Mexico Aging Study.[3]

Ageing and testicular function

As men age, the decrease in testicular function refers to a decline in either of the two major functions of the testes: testosterone production or sperm production.

Decline in serum testosterone

Both cross-sectional and longitudinal studies demonstrate a gradual decline in serum testosterone concentration starting after age 30 years. In older men, the changes in total testosterone are overshadowed by a more significant decline in free testosterone levels. This is a consequence of the age-associated increase in the levels of sex hormone-binding globulin (SHBG), which increases gradually as a function of age and binds testosterone with high affinity; less of the total testosterone is free.

In the European Male Ageing Study, a large cross-sectional study, the serum total testosterone concentration fell by 0.4% per year and the free testosterone concentration fell by 1.3% per year[4] between ages 40 and 79 years. Some of the effect of age was associated with obesity and comorbidities. In the Baltimore Longitudinal Study of Aging, the percentage of subjects with total testosterone concentrations in the hypogonadal range (total testosterone $<325\,\text{ng}\,\text{dl}^{-1}$) was 20, 30 and 50% for men in their 60s, 70s and 80s, respectively.[5] The rate of age-related decline in serum testosterone levels varies in different individuals and is affected by chronic disease such as obesity, new illness, serious emotional stress and medications.[6] There is evidence that many of these men are not symptomatic. An interesting observation from the MMAS was that half of the men found to have symptomatic androgen deficiency at one stage were found to be eugonadal when retested at a later stage.[7] This is probably because there is subject-to-subject variation in testosterone secretion and in the testosterone threshold where symptoms become manifest. The measurement of low testosterone in a patient should be reconfirmed at a later stage before considering treatment.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Decline in spermatogenesis

Characteristic age-related morphological testicular alternations occurs with ageing, such as decreased numbers of Leydig cells paralleling decreased testosterone production, arteriosclerotic lesions, thickening and hernia-like protrusions of the basal membrane of the seminiferi tubules and fibrotic thickening of the tunica albuginea. Surprisingly, these alterations do not lead to dramatic change with increasing age. Testicular size was somewhat larger.[8] Ejaculated sperm density increase, slightly with age, but the percentage motility was slightly greater in younger people. However, children of elderly fathers have a higher risk for autosomal dominant diseases, presumably due to increasing numbers of germ cell meioses and mitoses.

Diagnosis of late-onset hypogonadism

The diagnosis of LOH requires the presence of symptoms and signs suggestive of testosterone deficiency.[1] The testosterone deficiency can be caused by a combination of both primary and secondary hypogonadism. The symptom most associated with hypogonadism is low libido. Other manifestations of hypogonadism include erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density (BMD) and osteoporosis, mild anaemia, breast discomfort and gynaecomastia, hot flushes, sleep disturbance, body hair and skin alterations, decreased vitality and decreased intellectual capacity (poor concentration, depression, fatigue). The problem is that many of the symptoms of late-life hypogonadism are similar in other conditions or are physiologically associated with the ageing process. Depression, hypothyroidism and chronic alcoholism should be excluded, as should the use of medications such as corticosteroids, cimetidine, spironolactone, digoxin, opioid analgesics, antidepressants and antifungal drugs. Of course, diagnosis of LOH should never be undertaken during an acute illness, which is likely to result in temporarily low testosterone levels.

The Androgen Deficiency in Aging Male (ADAM) questionnaire (Table 100.1) and the Aging Male Symptoms Scale (AMS) may be sensitive markers of a low testosterone state (97 and 83%, respectively), but they are not tightly correlated with low testosterone (specificity 30 and 39%, respectively), particularly in the borderline low serum testosterone range. Therefore, questionnaires are not recommended for screening of androgen deficiency in men receiving healthcare for unrelated reasons. Moreover, healthy ambulatory elderly males over 70 years old, assessed by the AMS, had a high perception of sexual symptoms with mild psychological and mild to moderate somatovegetative symptoms. Note also that there is marked inter-individual variation of the testosterone level at which symptoms occur.

Table 100.1 Androgen Deficiency in Aging Male (ADAM) questionnaire[a].

1	Do you have a decrease in libido or sex drive?
2	Do you have a lack of energy?
3	Do you have a decrease in strength and/or endurance?
4	Have you lost weight?
5	Have you noticed a decreased 'enjoyment of life'?
6	Are you sad and/or grumpy?
7	Are your erections less strong?
8	Have you noticed a recent deterioration in your ability to play sports?
9	Are you falling asleep after dinner?
10	Has there been a recent deterioration in your work performance?

[a]A positive ADAM questionnaire was defined as 'yes' for questions 1 and 7 and 2–4 for all other items.

Hypogonadism in older men may be associated with chronic illnesses such as diabetes mellitus and renal disease. Systemic glucocorticoids can reduce testosterone biosynthesis in the testis and impact the hypothalamic–pituitary–gonadal (HPG) axis by inhibiting the release of luteinizing hormone (LH). Patients being treated with glucocorticoids for chronic conditions such as rheumatoid and osteoarthritic inflammation, skin inflammations, asthma, chronic obstructive pulmonary disease (COPD) and inflammatory bowel disease are at an increased risk for hypogonadism. COPD patients have a higher incidence of hypogonadism due to many factors, such as steroid treatment, chronic hypoxia and a systemic inflammatory response. Testosterone therapy can improve lean body mass, BMD and strength in hypogonadal men with COPD. Long-term use of opioids can lead to suppression of GnRH release by the hypothalamus, thereby inducing secondary hypogonadism, an entity called opioid-induced androgen deficiency (OPIAD). Androgen deficiency is strongly associated with AIDS wasting syndrome and testosterone therapy in HIV-positive hypogonadal men increases lean body and muscle mass and perceived wellbeing and decreases depression. Such chronic diseases should be investigated and treated.[9]

Laboratory diagnosis

Diagnosis of late-life hypogonadism requires both symptoms and low testosterone (Figure 100.1a). Careful clinical evaluations and repeated hormone measurements should be carried out to exclude transient decreases in serum testosterone levels such as those due to acute illnesses.

Serum testosterone has a diurnal variation; a serum sample should be obtained between 07.00 and 11.00 h. The most widely accepted parameter to establish the presence of hypogonadism is the measurement of serum total

testosterone. The ISA/ISSAM/EAU/EAA/ASA guidelines suggest that subjects with total testosterone levels above 350 ng dl^{-1} do not require substitution. Patients with serum total testosterone levels below 230 ng dl^{-1} will usually benefit from testosterone treatment. If the serum total testosterone level lies between 230 and 350 ng dl^{-1} (8–12 nmol l^{-1}) the patient could benefit from having a repeat measurement of total testosterone together with a measurement of SHBG concentrations so as to calculate free testosterone levels or bioavailable testosterone (BT, free plus albumin-bound), particularly in obese men.[10] The gold standard for BT measurement is by sulfate precipitation and equilibrium dialysis for free testosterone. However, usually neither technique is available in most laboratories so that calculated values seem preferable. Salivary testosterone, a proxy for unbound testosterone, has also been shown to be a reliable substitute for free testosterone measurements.[11]

One can calculate free testosterone reliably by using total testosterone, albumin and SHBG concentrations using an online calculator (http://www.issam.ch/freetesto.htm) or measure free testosterone accurately in a laboratory by equilibrium dialysis. As with total testosterone measurements, there is no general agreement as to what constitutes the lower limit of normal free testosterone levels, but the Endocrine Society mentions 50 pg ml^{-1} for free testosterone measured by equilibrium dialysis and the ISA, ISSAM, EAU, EAA and ASA recommend 65 pg ml^{-1} for calculated free testosterone.

The final step in determining whether a patient has primary or secondary hypogonadism is to measure the serum LH and follicle-stimulating hormone (FSH) (Figure 100.1b) Elevated LH and FSH levels suggest primary hypogonadism, whereas low or low-normal LH and FSH levels suggest secondary hypogonadism. Normal LH or FSH levels with low testosterone suggest primary defects in the hypothalamus and/or the pituitary (secondary hypogonadism). However, in elderly males, the rise in serum gonadotropin, FSH more than LH, is not as great as one would expect from the fall in testosterone, suggesting that the fall in testosterone with ageing is due more to secondary than primary hypogonadism. Unless fertility is an issue, it is usually not necessary to measure FSH and determining LH levels alone is sufficient. If the total testosterone concentration is <150 ng dl^{-1}, pituitary imaging studies and prolactin level are recommended to evaluate for structural lesions in the hypothalamic–pituitary region. Also, in secondary hypogonadism, prolactin levels should be obtained to rule out prolactinoma in addition to screening for haemochromatosis. A karyotype should be considered in a young teenager or infertile man with primary hypogonadism to diagnose Klinefelter syndrome (Figure 100.1b).

Treatment of late-onset hypogonadism

The principal goal of testosterone therapy is to restore the serum testosterone concentration to the normal range to alleviate the symptoms suggestive of the hormone deficiency. However, the ultimate goals are to maintain or regain the highest quality of life, to reduce disability, to compress major illnesses into a narrow age range and to add years to life.

Delivery systems

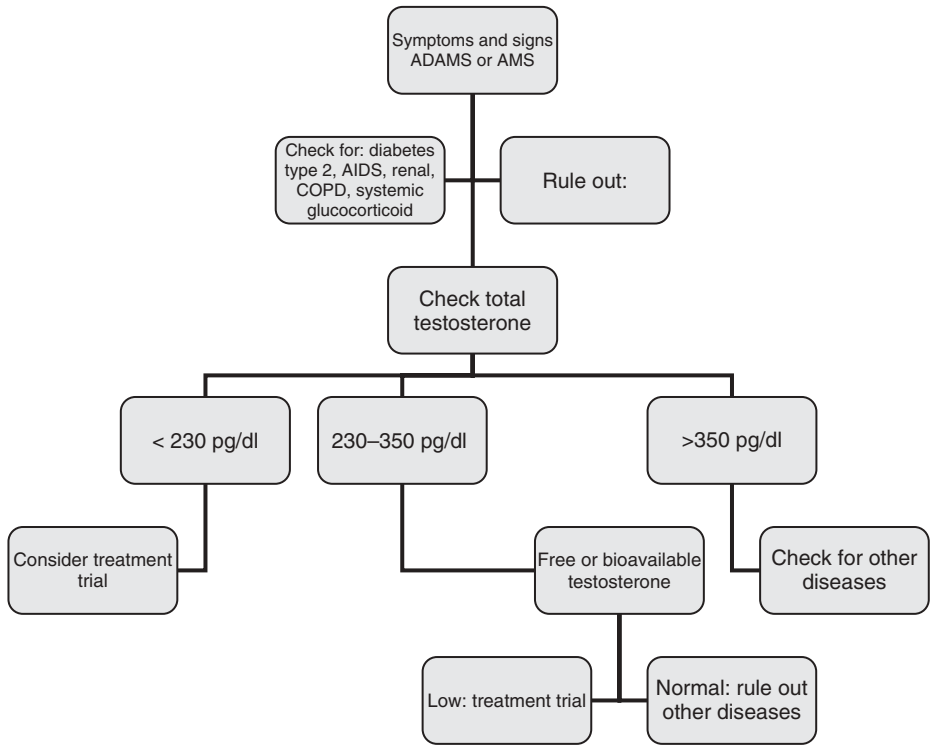
Several different types of testosterone replacement exist, including tablets, injections, transdermal systems, oral, pellets and buccal preparations of testosterone. Selective androgen receptor modulators (SARMs) are under development but not yet clinically available. The selection of the preparation should be a joint decision of an informed patient and physician. Short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with LOH. It is important to keep in mind that the goal of testosterone replacement therapy (TRT) is to increase blood testosterone concentrations to the normal (eugonadal) range and to match the most appropriate treatment to the individual patient. However, older males need higher levels to obtain a therapeutic benefit.

Oral agents

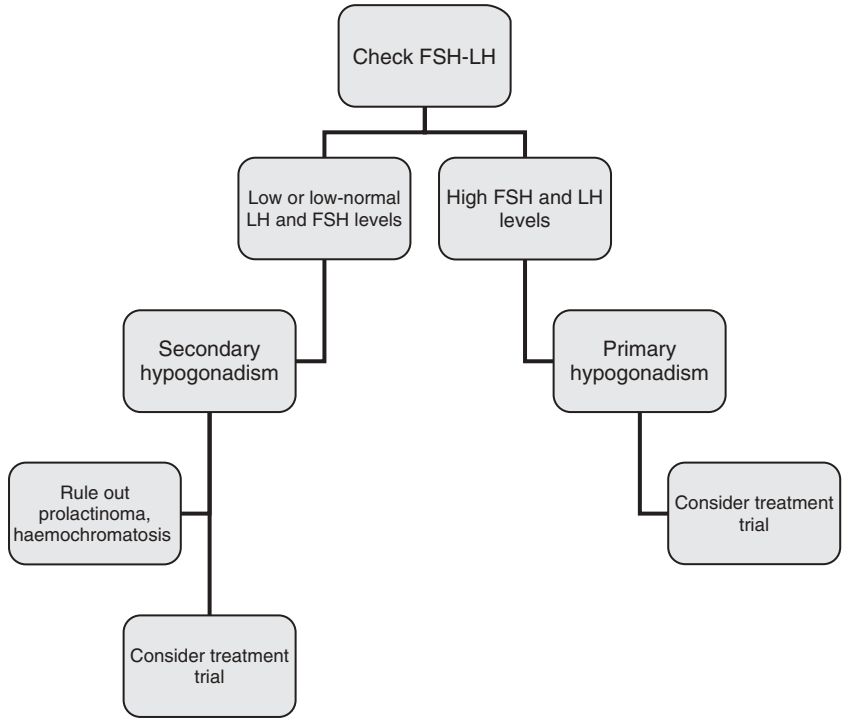
The modified testosterone 17α-methyltestosterone is an effective oral androgen formulation for hypogonadism; however, it is not recommended because of its hepatotoxic side effects and its potential liver toxicity, including the development of benign and malignant neoplasms in addition to deleterious effects on levels of both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). Oral testosterone undecanoate, however, bypasses first-pass metabolism through its preferential absorption into the lymphatic system. It is safe because of the lack of adverse liver side effects, but it is only available outside the USA.

Intramuscular injection

Testosterone cypionate and enanthate were frequently used for intramuscular injection of short-acting testosterone esters that usually produces supraphysiological peaks and hypogonadal troughs in testosterone levels, which result in fluctuations in energy, mood and libido in many patients corresponding to the fluctuations in serum testosterone levels. These fluctuations are more pronounced as the dosing interval is increased. The disadvantages are the need for deep intramuscular administration of an oily solution every 1–3 weeks and fluctuations in the serum



(a)



(b)

Figure 100.1 Diagnosis of hypogonadism.

testosterone concentration that result. A long-lasting formulation of testosterone undecanoate is available in the EU and other countries, but not yet in the USA. It consists of injections of 1000 mg of testosterone undecanoate at intervals of up to 3 months, offering an excellent alternative for substitution therapy of male hypogonadism. The serum testosterone concentration is maintained within the normal range.[12] However, the long duration of action creates a problem if there are complications of testosterone therapy. An oral formulation of this ester is also available in some countries, but it does not keep the serum testosterone concentration normal in hypogonadal men. Note that the intramuscular injections of testosterone can cause local pain, soreness, bruising, erythema, swelling, nodules or furuncles.

Transdermal systems

Transdermal testosterone is available in either a scrotal or a non-scrotal skin patch and more recently as a gel preparation, allowing a single application of this formulation to provide continuous transdermal delivery of testosterone for 24 h, producing circulating testosterone levels that approximate the normal levels (e.g. 300–1000 ng dl^{-1}) seen in healthy men. Daily application is required for each of these. They are designed to deliver 5–10 mg of testosterone per day and result in normal serum testosterone concentrations in the majority of hypogonadal men.[13] Scrotal patches produce high levels of circulating dihydrotestosterone (DHT) due to the high 5α-reductase enzyme activity of scrotal skin, but these are not so popular because the scrotum has to be shaved and the adherence is not good. Non-genital patches are applied once per day to the back, abdomen, thighs or upper arms. Skin irritation can occur and preapplication of a corticosteroid cream can help reduce this. The transdermal gels are colourless hydroalcoholic gels containing 1–2% testosterone. They are applied once per day to the skin. There is a lower incidence of skin irritation compared with the patch, but testosterone can be transferred from the patient to his partner or to children after skin contact. This risk can be minimized by covering the site of application with clothing after the gel has dried, by washing the application site when skin-to-skin contact is expected and by having patients wash their hands with soap and water after applying the gel. A reservoir-type transdermal delivery system for testosterone was developed using an ethanol–water (70:30) cosolvent system as the vehicle. This device is available in Europe as a body patch without reservoir and applied every 2 days. The advantages include ease of use and maintenance of relatively uniform serum testosterone levels over time, resulting in maintenance of relatively stable energy, mood and libido, in addition to the efficacy in providing adequate TRT.

Sublingual and buccal

Cyclodextrin-complexed testosterone sublingual formulation is absorbed rapidly into the circulation, where testosterone is released from the cyclodextrin shell. This formulation has been suggested to have good therapeutic potential, after adjustment of its kinetics, to produce physiological levels of testosterone.

A mucoadhesive buccal testosterone sustained-release tablet, delivering 30 mg, applied to the upper gum just above the incisor teeth, has been shown to restore serum testosterone concentrations to the physiological range within 4 h of application, with steady-state concentrations achieved within 24 h of twice-daily dosing and achieves testosterone levels within the normal range. Studies indicate that Striant is an effective, well-tolerated, convenient and discreet treatment for male hypogonadism. However, it has had minimal clinical uptake, owing to the difficulty of maintaining the buccal treatment in the mouth.[14] The incidence of adverse effects is low, although gum and buccal irritation and alterations in taste have been reported.

Subdermal implants

Subcutaneous pellets were among the earliest effective formulations for administering testosterone. Although not frequently used, they remain available. The testosterone pellets are usually implanted under the skin of the lower abdomen using a trochar and cannula or are inserted into the gluteus muscle. Six to ten pellets are implanted at one time and they last 4–6 months, when a new procedure is required to implant more. Testosterone pellets currently are the only long-acting testosterone treatment approved for use in the USA.

Subdermal testosterone implants still offer the longest duration of action with prolonged zero-order, steady-state delivery characteristics. The standard dosage is four 200 mg pellets (800 mg) implanted subdermally at intervals of 5–7 months.[15] However, the *in vivo* testosterone release rate of these testosterone pellets and its determinants have not been studied systematically. As a result of their long-lasting effect and the inconvenience of removing them, the risk of infection at the implant site and extrusion of the pellets which occurs in 5–10% of cases even with the most experienced, their use is limited only to men for whom the beneficial effects and tolerance of TRT have already been established.

Intranasal testosterone

Testosterone is well absorbed after nasal administration.[16] Application of MPP-10 results in a more pulse-like testosterone profile rather than the relatively sustained

serum levels attained with transdermal administration. The intranasal drug delivery system represents a mechanism to proximate more closely the normal circadian variation of testosterone levels, in contrast to the abnormal steady-state levels seen with transdermal products or the large fluctuations over longer periods of time seen with injections. Further studies are necessary to determine the effect of nasal testosterone application in hypogonadal men over prolonged periods of time.

Benefits of testosterone replacement therapy

Restoring testosterone levels in older male patients to within the normal range by using TRT can improve many of the effects of hypogonadism. Most importantly, these include beneficial effects on mood, energy levels and patients' sense of wellbeing, sexual function, lean body mass and muscle strength, erythropoiesis, BMD, cognition and some benefits on cardiovascular risk factors. These are summarized in Table 100.2.

Improved sexual desire, function and performance

The prevalence of erectile dysfunction increases markedly with age. Sexual function, measured by frequency of orgasm or intercourse or by sexual satisfaction, is lower in elderly men than in young men. Men with hypogonadism due to known disease also have a decline in sexual function, as illustrated by an improvement after testosterone treatment. Serum free testosterone was significantly correlated with erectile and orgasmic function domains of the International Index of Erectile Function (IIEF) questionnaire. Men with greater sexual activity had higher bio-T levels than men with a lower frequency and androgen deficiency may contribute to the age-related decline in male sexuality; correspondingly low levels of bio-T were associated with low sexual activity. Compared with younger men, elderly men require higher levels of circulating testosterone for libido and erectile function. However, erectile dysfunction and/or diminished libido with or without a testosterone deficiency might be related to other comorbidities or medications.

Table 100.2 Potential benefits of TRT.

- Improved sexual desire and function
- Increased BMD
- Improved mood, energy and quality of life
- Changed body composition and improved muscle mass and strength
- Improved cognitive function

Men with erectile dysfunction and/or diminished libido and documented testosterone deficiency are candidates for testosterone therapy. Randomized controlled clinical trials indicate some benefits of testosterone therapy on sexual health-related outcomes in hypogonadal men.[17] Testosterone replacement has also been shown to enhance libido and the frequency of sexual acts and sleep-related erections. Transdermal TRT, in particular, has been linked to positive effects on fatigue and mood, which affect sexual activity.

A short therapeutic trial may be tried in the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels. An inadequate response to testosterone treatment requires reassessment of the causes of the erectile dysfunction. There is evidence that the combined use of testosterone and phosphodiesterase type 5 inhibitors in hypogonadal or borderline eugonadal men have a synergetic effect.[18] The combination treatment should be considered in hypogonadal patients with erectile dysfunction failing to respond to either treatment alone.

The role of testosterone supplementation in men with erectile dysfunction who are not androgen deficient or in the low-normal range needs further investigation to determine whether TRT will improve erectile function. Failure of improvement when the serum testosterone concentration has been restored to normal suggests another cause of the symptoms.

Bone mineral density

As men age, their BMD declines. Osteoporosis is an underrecognized problem in men. Testosterone plays a major role in BMD. Osteopenia, osteoporosis and fracture prevalence rates are greater in hypogonadal older men. In nursing homes, of elderly men who have experienced hip fractures, 66% are hypogonadal. Patients with prostate cancer treated with androgen deprivation therapy have an increased risk of osteoporotic fracture. Assessment of bone density at 2 year intervals is advisable in hypogonadal men and serum testosterone measurements should be obtained in all men with osteopenia. All persons with low testosterone should have their 25-hydroxyvitamin D levels measured and replaced if low.

Testosterone produces this effect by increasing osteoblastic activity and through aromatization to estrogen reducing osteoclastic activity. The role of the partial androgen deficiency in ageing males in bone fracture rate remains to be established. The correlation with bioestradiol, the levels of which decline in elderly males, was even stronger, suggesting that part of the androgen effects on bone are at least partially indirect, mediated via their aromatization.[19] An increase in osteocalcin levels, an index of osteoblast activity, was observed and a decrease in hydroxyproline excretion, an index of bone resorption, was also noted.

Trials of the effects of TRT on BMD yielded mixed results. Increases in spinal bone density have been realized in hypogonadal men, with most treated men maintaining bone density above the fracture threshold. An improvement in both trabecular and cortical BMD of the spine was seen, independent of age and type of hypogonadism; in addition, a significant increase in paraspinal muscle area has been observed, emphasizing the clinical benefit of adequate replacement therapy for the physical fitness of hypogonadal men. The pooled results of a meta-analysis suggest a beneficial effect on lumbar spine bone density and equivocal findings on femoral neck BMD. Trials of intramuscular testosterone reported significantly larger effects on lumbar bone density than trials of transdermal testosterone, particularly among patients receiving chronic glucocorticoids.[20] In eugonadal men with osteoporosis, testosterone esters (250 mg per 2 weeks) gave mixed results. Although there is significant evidence of an association between hypogonadism and osteoporosis, studies of TRT in men with osteoporosis are limited and none have used fractures as an end-point.

Improved body composition and muscle mass and strength

There is a significant change in body composition characterized by decreased fat free mass and increased and redistributed fat mass in elderly patients. These changes can impose functional limitations and increase morbidity. In men, declining testosterone levels that occur with ageing can be a contributing factor to these changes through a direct effect on muscle cells by testosterone or by stimulating IGF-1 expression directly and indirectly, leading to increased muscle protein synthesis and growth. Epidemiological studies have demonstrated a correlation between BT concentrations and fat-free mass; however, the correlation with grip strength is not clear.

Testosterone replacement may be effective in reversing age-dependent body composition changes and associated morbidity. Testosterone administration improves body composition with a decrease in fat mass and increase in lean body mass, but the body weight changes do not differ significantly.[21] Changes in lower-extremity muscle strength and measures of physical function were inconsistent among studies. Some studies showed a positive correlation between testosterone and muscle strength parameters of the upper and lower extremities, as measured by leg extensor strength and isometric hand grip strength, and also functional parameters, including the doors test, get up and go test and five-chair sit/stand test.[22] On the other hand, some reported an increase in lean body mass but no change in physical function or an increase in strength of knee extension or flexion.

It is not clear whether testosterone replacement in frail older men with low testosterone levels can improve physical function and other health-related outcomes or reduce the risk of disability, falls or fractures. A combination of testosterone and a nutritional supplement markedly reduced hospital admissions in older men and women.

Mood, energy and quality of life

Hypogonadal older men commonly complain of loss of libido, dysphoria, fatigue and irritability.[71] These symptoms overlap with signs and symptoms of major depression. There is significant correlation between BT, reduced feelings of wellbeing and a depression score in elderly men, independent of age and weight, but not with total testosterone levels.

TRT has variable effects on mood, energy, fatigue, irritability and sense of wellbeing. The results of placebo-controlled randomized trials on testosterone's effect on quality of life and depressive mood were inconsistent across trials and imprecise. Testosterone administered to non-depressed eugonadal men in physiological doses did not have effect on mood.[23] Administration of supraphysiological doses of testosterone to eugonadal men has been associated with mania in a small proportion of patients. Testosterone replacement of hypogonadal men with major depressive disorder might be an effective antidepressant or augmentation to partially effective antidepressant.[24] Testosterone gel had significantly greater improvement as augmentation therapy for depressive symptoms than subjects receiving placebo in hypogonadal men with selective serotonin reuptake inhibitor (SSRI) partial response. These significant correlations with testosterone levels were only observed when the levels were below the normal range, which suggests that once a minimally adequate testosterone/DHT level was achieved, further increase did not contribute further to improvement of mood. However, the studies reported tend to be of limited size and duration, with a lack of large-scale trials with extended long-term follow-up. This effect may be a direct effect of testosterone or related to positive effects of testosterone on weight and/or other anthropometric indices.

On the other hand, the testosterone–placebo difference distinguishable with respect to mood was not consistent. No relationship between testosterone level and depressive symptoms was found in the MMAS. This discrepancy in the results of the effects of TRT on mood may be explained by the genetic polymorphism in the androgen receptor which defines a vulnerable group in whom depression is expressed when testosterone levels fall below a particular threshold.

Finally, testosterone treatment must be considered experimental. More controlled studies using exogenous testosterone for depression in elderly men are needed. The best

candidates for treatment may be hypogonadal men who are currently taking an existing antidepressant with inadequate response.

Cognitive function

Dementia is a major problem for older men. The decrease in serum testosterone concentrations that occurs with ageing in men may be associated with a decline in verbal and visual memory and visuospatial performance and a faster rate of decline in visual memory. Men with a higher ratio of total testosterone to SHBG predict a reduced incidence of Alzheimer's disease and patients with Alzheimer's disease had a lower ratio of total testosterone to SHBG compared with age-matched controls.[25] Low BT is strongly associated with amnestic mild cognitive impairment and higher bioavailable and free testosterone concentrations have each been associated with better performance in specific aspects of memory and cognitive function, with optimal processing capacity found in men ranging from 35 to 90 years of age even after adjustment for potential confounders including age, educational attainment and cardiovascular morbidity; whereas total testosterone was not.[26]

On the other hand, contradictory findings have also been reported between total or free testosterone and measures of working memory, speed/attention or spatial relations in older men. No association was found between lower free testosterone levels and higher performance on spatial visualization tasks and between higher free and total testosterone levels and poorer verbal memory and executive performance; however, there is a correlation with faster processing speed.[27] A possible source of conflicting results in these studies may stem from interactions between testosterone levels and other risk factors for cognitive impairment such as apolipoprotein E4 genotype and systemic illness that cause low testosterone.

In men undergoing hormonal therapy for prostate cancer, suppression of endogenous testosterone synthesis and blockade of the androgen receptor resulted in a beneficial effect on verbal memory but an adverse effect on spatial ability slowed reaction times in several attentional domains; plasma amyloid levels increased as T levels decreased. Discontinuation of treatment resulted in improved memory but not visuospatial abilities. One of the possible protective mechanisms of action of testosterone would be through its conversion into estradiol (E2), the most potent estrogen, which could exert protective effects on the brain structures in ageing patients.

Trials of TRT in men to evaluate its effects on measures of cognitive function and memory to date were all relatively small and of a relatively short duration and have shown mixed results. Androgen supplementation in elderly hypogonadal men improves spatial cognition and verbal fluency and in elderly men without dementia it may reduce working memory errors. Intramuscular testosterone improved verbal and spatial memory and constructional abilities in non-hypogonadal men with mild cognitive impairment and Alzheimer's disease. On the other hand, in Alzheimer's disease patients, testosterone treatment appeared to improve quality of life and verbal memory without imprecise effects on several dimensions of cognition.

Therefore, although the evidence from studies is not uniform, lower free testosterone appears to be associated with poorer outcomes on measures of cognitive function, particularly in older men, and TRT in hypogonadal men may have some benefit for cognitive performance.

Effect on metabolic syndrome and cardiovascular risk factors

Testosterone has a positive effect on reducing the risk factors for the metabolic syndrome and cardiovascular disease. The increased correlation between low testosterone levels and the severity of coronary artery disease may be related to the fact that low androgen levels are accompanied by an accumulation of abdominal visceral fat, which is known to be associated with increased cardiovascular risk factors,[28] impaired glucose tolerance and non-insulin-dependent diabetes mellitus (syndrome X). Low endogenous testosterone concentrations are related to mortality due to cardiovascular disease and all causes.

There is a relationship between testosterone levels and body mass index (BMI), waist circumference, waist–hip ratio, serum leptin, LDL-C, triglyceride and fibrinogen levels, hypertension, diabetes. At the same time, adipose tissue affects testosterone levels by increasing the aromatization of testosterone to estradiol, which provides negative feedback on the HPG axis and by decreasing testosterone levels via a decrease in SHBG levels. Thus, adiposity potentially leads to hypogonadism, which itself promote further adiposity.

Low testosterone concentrations are known to occur in association with type 2 diabetes. Prevalence in diabetic men has been estimated at 33–50%. There is no relation between the degree of hyperglycaemia and testosterone concentration. Prostate-specific antigen (PSA) is significantly lower in type 2 diabetics and this is related to their lower plasma testosterone concentrations.[29] Low testosterone concentrations predict the development of type 2 diabetes. Testosterone also may suppress insulin resistance independently of its effects on adiposity. In addition, diet and exercise increased testosterone levels in hypogonadal men with metabolic syndrome and newly diagnosed type 2 diabetes.

The effect of androgen replacement in elderly men on LDL-C and HDL-C is controversial. The relationship between testosterone and HDL is confounded by the fact that both HDL and testosterone are inversely related to BMI.

Data from the MMAS have demonstrated that low total or free testosterone correlates with low HDL-C. Testosterone replacement therapy in men with hypogonadism has little effect on serum concentrations of total cholesterol and LDL-C. HDL-C levels decrease in patients on oral testosterone therapy but not when given as a transdermal gel to hypogonadal men. In a meta-analysis of 10 studies of intramuscular testosterone esters and plasma lipids in hypogonadal men, a small, dose-dependent decrease was seen in total cholesterol, LDL-C and HDL-C.[30] The mechanism of the fall in lipids might be related to the decrease in the visceral abdominal fat mass under the influence of androgens, which inhibit lipoprotein lipase activity and increase lipolysis with improvement of insulin sensitivity and mobilization of triglycerides from abdominal fat tissue. Note that supraphysiological testosterone levels induce an increase in LDL-C and a decrease of HDL-C and may increase the risk of cardiovascular disease.

Testosterone treatment in elderly patients with chronic heart failure might improve insulin sensitivity and various cardio-respiratory and muscular outcomes. The administration of testosterone at physiological concentration increases coronary blood flow in patients with coronary heart disease. Transdermal TRT was found to be beneficial for men with chronic stable angina as they had greater angina-free exercise tolerance than placebo-treated controls. However, no consistent relationship between the levels of free or total testosterone and coronary atherosclerosis in men undergoing coronary angiography has been observed.

Improving anaemia

Endogenous androgens are known to stimulate erythropoiesis and increase reticulocyte count, blood haemoglobin levels and bone marrow erythropoietic activity in mammals, whereas castration has opposite effects. Testosterone deficiency results in a 10–20% decrease in the blood haemoglobin concentration, which can result in anaemia. The main androgen involvement in the mechanism of normal haematopoiesis is thought to be direct stimulation of renal production of erythropoietin by testosterone. Moreover, the latter may also act directly on erythropoietic stem cells.

Risks of testosterone replacement therapy

The risks of TRT depend upon age, life circumstances and other medical conditions. There is a risk for prostate cancer and worsening symptoms of benign prostatic hypertrophy, liver toxicity and tumour, worsening symptoms of sleep apnoea and congestive heart failure, gynaecomastia, infertility and skin diseases. TRT is not appropriate for men who are interested in fathering a child because exogenous testosterone will suppress the hypothalamic–pituitary–thyroid (HPT) axis. The risks of TRT are summarized in Table 100.3.

Table 100.3 Potential risks for TRT in elderly men.

- Stimulates growth of prostate cancer and breast cancer
- Worsens symptoms of benign prostatic hypertrophy
- Causes liver toxicity and liver tumour
- Causes gynaecomastia
- Causes erythrocytosis
- Causes testicular atrophy and infertility
- Causes skin diseases
- Causes or exacerbates sleep apnoea

The prostate and testosterone replacement therapy

In ageing men with LOH, TRT may normalize serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions and causes no significant adverse effects on the prostate. At present, there is no conclusive evidence that TRT increases the risk of prostate cancer or benign prostatic hyperplasia (BPH).

Benign prostatic hyperplasia

With ageing, some men experience an exacerbation of BPH symptoms; predominantly lower urinary tract symptoms (LUTS) due to urinary outflow obstruction. The testosterone dependence of BPH has been known for a long time. Testosterone supplements increase prostate volume with, eventually, a mild increase in PSA levels in old men. Although a meta-analysis showed that the total number of prostate events combined was significantly greater in testosterone-treated men than in placebo-treated men, the majority of events are due to prostate biopsy. At the same time, many studies have failed to show significant exacerbation of voiding symptoms attributable to BPH during testosterone supplementation and complications such as urinary retention have not occurred at higher rates than in controls receiving placebo, nor has there been any difference in the urine flow rates, post-voiding residual urine volumes and prostate voiding symptoms with patients receiving treatment in these studies. The poor correlation between prostate volume and urinary symptoms explains this illogicality. There are no compelling data to suggest that testosterone treatment exacerbates LUTS or promotes acute urinary retention. However, severe LUTS, due to BPH, represent a relative contraindication which is no longer applicable after successful treatment of lower urinary tract obstruction. The patient needs to be made aware that there might be increased voiding symptoms during treatment.

Prostate cancer

Prostate cancer is well known to be, in the majority of cases, an androgen-sensitive disease and prostate cancer has been treated in patterns designed to lower the testosterone level; androgen replacement therapy is an absolute contraindication. The prevalence of prostate cancer in many studies on patients receiving TRT was similar to that in the general population. So far, there is no compelling evidence that testosterone has a causative role in prostate cancer. There is, however, unequivocal evidence that testosterone can stimulate growth and aggravate symptoms in men with locally advanced and metastatic prostate cancer. A fuller explanation may be that prostate cancer is very sensitive to changes in serum testosterone when at low concentrations, but is insensitive at higher concentrations because of saturation of the androgen receptors. Men successfully treated for prostate cancer and diagnosed with hypogonadism are candidates for testosterone replacement after a prudent interval if there is no clinical or laboratory evidence of residual cancer.[31] In addition, no effect was found of TRT on PSA levels and the changes in PSA were not influenced by the mode of TRT, patient age or baseline levels of PSA or testosterone. It is important to mention that the occurrence of prostate cancer and PSA concentrations are lower in patients with type 2 diabetes and related to testosterone concentrations. It is not yet known if the normal PSA reference ranges should be lowered for men with type 2 diabetes.

In summary, there is no convincing evidence that the normalization of testosterone serum levels in men with prostate problems and low levels is deleterious. TRT can be cautiously considered in selected hypogonadal men treated with curative intent for prostate cancer and without evidence of active disease.

Liver problems

Benign and malignant hepatic tumours, intrahepatic cholestasis, hepatotoxicity and liver failure have been reported with TRT. These unfavourable hepatic effects do not appear to be associated with transdermal or intramuscular injections. For this reason, the oral forms of testosterone, with the exception of testosterone undecanoate, are discouraged. Other liver abnormalities associated with TRT include peliosis hepatis, hepatocellular adenoma and carcinoma.

Sleep apnoea

Sleep apnoea was worse in men with hypogonadism treated with testosterone. In contrast, in a recent meta-analysis, the frequency of sleep apnoea did not differ between testosterone and placebo-treated men. Physicians should inquire about symptoms, such as excessive daytime sleepiness and witnessed apnoea during sleep by a partner, and if indicated, polysomnography should be performed.

Erythrocytosis

There is a correlation between high testosterone levels and high haemoglobin. Erythrocytosis is a common adverse effect of testosterone administration. Testosterone-treated men were almost four times more likely to have a haematocrit >50%. Erythrocytosis can develop during testosterone treatment, especially in older men treated by injectable testosterone preparations. The elevation in haemoglobin above certain levels may have had a greater overall mortality and cardiovascular mortality, particularly in the elderly, because the increase in blood viscosity could exacerbate vascular disease in the coronary, cerebrovascular or peripheral vascular circulation, especially in people with other diseases that cause secondary polycythaemia, such as chronic obstructive pulmonary disease. Testosterone dosage correlates with the incidence of erythrocytosis and polycythaemia is related most of the time to supraphysiological levels.

Periodic haematological assessment is indicated (e.g. before treatment, then at 3–4 months and at 12 months in the first year of treatment and annually thereafter). Although it is not yet clear what critical threshold is desirable, dose adjustment and/or periodic phlebotomy may be necessary to keep the haematocrit below 52–55%.

Other side effects of TRT

Supraphysiological doses of androgens may cause decreased testicular size, acne and azoospermia. The decrease in testicular size and compromised fertility during TRT occur because of the down regulation of gonadotropins. It is related to aromatization of testosterone into estradiol in peripheral fat and muscle tissue. Even the ratio of estradiol to testosterone usually remains normal. It occurs especially with testosterone enanthate or cypionate. Dose adjustment may be necessary. Gynaecomastia is another benign complication of testosterone treatment.

TRT has been associated with exacerbation of sleep apnoea. The effect of testosterone is not on the dimensions of the upper airway, but it most likely contributes to sleep disorder breathing by central mechanisms. The development of signs and symptoms of obstructive sleep apnoea during testosterone therapy warrants a formal sleep study and treatment with continuous positive airway pressure (CPAP) if necessary. If the patient is unresponsive or cannot tolerate CPAP, the testosterone must be reduced or discontinued. Testosterone is anabolic and it will cause some nitrogen, sodium and water retention. Oedema may

be worsened in patients with pre-existing cardiac, renal or hepatic disease. Hypertension has rarely been reported.

Symptom relief

The time course of the effects of testosterone replacement is variable. Once testosterone levels are restored to a stable normal range, there is an improvement in libido, sexual function, mood and energy levels, insulin resistance and fat-free mass relatively early in the course of treatment. The reduction in fat body mass, an increase in lean body mass and an improvement in BMD at the hip and spine started after a period between 6 and 24 months.

Monitoring patients on TRT

Patients who are treated with testosterone should be monitored to determine that normal serum testosterone concentrations are being achieved. If the patient has primary hypogonadism, normalization of the serum LH concentration should also be used to judge the adequacy of the testosterone dose, no matter which testosterone preparation is used. They should be monitored for both desirable and undesirable effects.

Once TRT has started, patients need to be carefully monitored. Patients should be monitored for signs of oedema, gynaecomastia, sleep apnoea, LUTS and low BMD. Laboratory parameters should be monitored before and during treatment. There are clinical practice guidelines from the Endocrine Society for monitoring patients receiving TRT. Testosterone level, digital rectal examination, PSA, haematocrit, BMD, lipids and liver function tests should be checked at baseline, then the patient should be evaluated 3 and 6 months after treatment starts and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects. If the haematocrit is more than 54%, therapy should be stopped until the haematocrit decreases to a safe level; the patient should be evaluated for hypoxia and sleep apnoea; therapy should then be reinitiated with a reduced dose. BMD of lumbar spine and/or femoral neck should be measured at baseline every 1–2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture.

Testosterone levels should be monitored 3 months after initiation of TRT. A mid-morning total serum testosterone level should be obtained. A target range of 400–500 ng dl^{-1} (14.0–17.5 nmol l^{-1}) for older men is suggested. However, if there is no symptomatic response, higher levels may be necessary. For injectable testosterone, the serum level can be measured between injections. For men treated with a transdermal testosterone patch, the serum level should be measured 3–12 h after patch application. In patients receiving buccal testosterone tablets, the serum level should be measured immediately before application of a fresh system. Patients on testosterone gel may have levels checked any time after at least 1 week of therapy. In all cases, BT levels should also be monitored as testosterone therapy lowers SHBG.

For patients with BPH, LUTS should be assessed by the International Prostate Symptom Score (IPSS). For prostate cancer, digital rectal examination and measurement of serum PSA should be performed before initiating testosterone replacement, 3 months after initiation of treatment and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the patient. All men who present for TRT should undergo prostate biopsy if they have an abnormal PSA level or abnormal result on digital rectal examination with low threshold to do or repeat prostate biopsy if the PSA level or digital rectal examination changes. The American Urological Association (AUA) suggests a urological consultation for any of the following: if the patient has an abnormal digital rectal examination result, if the PSA levels exceed 2.5 ng ml^{-1} in males under 60 years or 4 ng ml^{-1} in men over 60 years, or a velocity change of 0.75 ng ml^{-1} or greater in a year.[32]

The use of testosterone preparations should be discussed with the patient, who should be closely monitored for efficacy and toxicities. Failure to benefit from clinical manifestations should result in discontinuation of treatment after 3 months for libido and sexual function, muscle function and improved body fat, and a longer interval for BMD. Further investigations for other causes of symptoms are then mandatory.

Precautions and contraindications for TRT

Healthcare providers must rule out contraindications to treatment before starting patients on TRT (Table 100.4). The presence of a clinical prostatic carcinoma is an absolute contraindication for TRT and should be carefully excluded by PSA, rectal examination and, eventually, biopsy before starting any therapy. There is also no clear recommendation for men successfully treated for prostate cancer who would be potential candidates for testosterone substitution after a 'prudent' interval if there is no clinical or laboratory evidence of residual cancer.

The presence of breast cancer is also a contraindication for TRT, and also a prolactinoma, as their growth may be stimulated by TRT. A very high risk of serious adverse outcomes, undiagnosed prostate nodules or indurations, unexplained PSA elevation, erythrocytosis (haematocrit >50%), severe LUTS with benign prostatic hyperplasia with an IPSS >19, unstable congestive heart failure (class III or IV) and untreated obstructive sleep apnoea are

Table 100.4 Contraindications for TRT.

- Very high risk of serious adverse outcomes
- Prostatic carcinoma
- Breast cancer
- Prostate nodules or indurations
- Unexplained prostate-specific antigen (PSA) elevation
- Erythrocytosis (haematocrit >50%)
- Severe lower urinary tract symptoms with benign prostatic hyperplasia with an International Prostate Symptom Score (IPSS) >19
- Unstable congestive heart failure (class III or IV)
- Severe untreated sleep apnoea

considered as moderate to high risk factors for potential adverse outcomes.[33]

Conclusion and recommendations

The decrease in the major function of the testes, late-onset hypogonadism, is a common condition in the male population but it is still underdiagnosed and undertreated. The apparently increasing incidence and expanding range of treatment options may facilitate greater awareness of the condition. The symptoms in the elderly have a complex origin. It may be reasonably assumed that the age-associated decrease in testosterone levels is in part responsible for the symptoms of ageing. In the absence of known pituitary or testicular disease, we suggest TRT only for older men with low serum testosterone concentrations and clinically important symptoms of androgen deficiency. The benefits and risks of TRT must be clearly discussed with the patient and an assessment of the major risk factors made before commencing testosterone treatment. The major contraindication for androgen supplementation is the presence of a prostatic carcinoma. The response to testosterone treatment should be assessed. If treatment is undertaken, the patient should be screened before treatment and monitored during treatment for evidence of testosterone-dependent diseases. The target serum testosterone concentration in older men should be lower than that for younger men, for example, 300–400 rather than 500–600 ng dl^{-1}, to minimize the potential risk of testosterone-dependent diseases.[34]

If there is no improvement of symptoms and signs, treatment should be discontinued and the patient investigated for other possible causes of the clinical presentations. Many questions in the treatment of hypogonadism remain unanswered and there is a need for large clinical trials to assess the long-term benefits and risks of TRT in older men with LOH.

Key points

- Secondary hypogonadism occurs in at least 20% of older males.
- Testosterone replacement improves libido, potency, ejaculate volume, bone mineral density, erythropoiesis and cognition.
- Testosterone replacement increases muscle mass and decreases fat mass.
- Testosterone replacement techniques include patches, gels, injections and subdermal implants

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CHAPTER 101

Diabetes mellitus

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Introduction

Diabetes care systems for older people require an integrated multidimensional approach involving general practitioners, hospital specialists and other members of the healthcare team. There should be an emphasis on diabetes prevention and its complications, early treatment for vascular disease and functional assessment of disability due to limb problems, eye disease and stroke.

Inequalities of care are common in many healthcare systems due to variations in clinical practice, particularly in relation to older people. This may be manifest as a lack of access to services, inadequate specialist provision, poorer clinical outcomes and patient and family dissatisfaction. The recent development of clinical guidelines that are responsive to the needs of older people with diabetes may be an important step to minimize deficits in care from country to country, worldwide.

Type 2 diabetes mellitus is a common disabling chronic cardiovascular and medical disorder that has a tremendous health, social and economic burden and has a high prevalence of 10–30% in subjects above 65 years of age across Europe. About 60% of total healthcare expenditure on diabetes in this special group can be accounted for by acute-care hospitalizations and compared with non-diabetic counterparts, the relative risk for admission to hospital is 5.0. At any one time, about one in 12 district hospital beds is occupied by older people who have diabetes and their length of stay is double that of non-diabetic inpatients. The introduction of insulin to their regimen results in a quadrupling of expenditure, presumably because of the additional resources required in both hospital and community settings to monitor and support the use of insulin.

A direct approach to the metabolic management of type 2 diabetes in older subjects is to concentrate on strategies designed to limit and ameliorate both defective insulin secretion and insulin resistance. Type 2 diabetes represents a cluster of cardiovascular risk factors that pose a significant vascular threat and, in ageing subjects, the added effects of ageing and renal impairment increase the impact of this syndrome, and some of the features may be present up to 10 years before the onset of overt hyperglycaemia, thus increasing the cardiovascular risk before the onset of diabetes. Since up to 50% of the variability in insulin action in insulin-resistant states may be associated with lifestyle differences such as obesity, physical activity levels and cigarette smoking, it becomes obvious that environmental, preventative and health promotional strategies are of vital importance in limiting the impact of this epidemic.

Management of diabetes in older people can be relatively straightforward, especially when patients have no other comorbidities and when vascular complications are absent. In many cases, however, special issues arise that increase the complexity of management and lead to difficult clinical decision-making. It is therefore not surprising that the present state of diabetes care for older patients varies throughout Europe and North America. Although *geriatric diabetes* is developing as a subspeciality interest in the UK, there is little evidence of its presence in other national diabetes care systems and virtually no specific provision for those who are housebound or in institutional care. This chapter can be considered to be a learning programme that aims to provide a succinct but comprehensive review of diabetes care for older people, focusing on special areas of concern.

We have identified two principal aims: (1) to develop and enhance the knowledge and application of the principles of diabetes and diabetes care in older persons and (2) to provide clinicians with the knowledge and skills and to influence attitudes to maximize their effectiveness in applying this learning within their own clinical setting. In addition, we have suggested that clinicians who study this chapter in depth should be able to demonstrate (1) an in-depth understanding of diabetes in older people and to analyze their own organization's provision and care, with

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a view to enhancing local care; and (2) an understanding of the means by which the diabetes care team in their own organization and key players in their own community can be engaged in improving the quality of diabetes care for older people. Further goals might include the ability to (3) reflect on their personal learning and apply that learning to the approaches they take with team members, other care professionals, patients and carers, and (4) analyse and evaluate outcomes in the delivery of care to older people who have diabetes, taking into account the roles of other care professionals and the beliefs of people from different ethnic and cultural backgrounds.

Epidemiology, pathogenesis and modes of presentation

The WHO estimates that in 2011 there are around 350 million individuals with diabetes worldwide, and that number is projected to increase to over 450 million by 2030. Several important risk factors (Table 101.1) are likely to underpin this increase in prevalence, such as advancing age of the population, greater numbers of people from ethnic minority backgrounds adopting a 'transitional' lifestyle, greater levels of overweight and obesity and more sedentary lifestyles. From an epidemiological perspective, ageing is an important factor: in the USA, the number of people with diabetes aged 75 years and over doubled between 1980 and 1987. In most populations, peak rates are generally found in the sixth decade and subsequently, although in Pima Indians the peak rate is between the fourth and fifth decades.

Most developed countries have a prevalence rate of about 17% in white elderly subjects and 25% in non-white subjects. The prevalence in white British elderly is only around 9% although the prevalence in non-white British elderly is about 25% and the prevalence in British care homes is 25%.

There is an increasing view that diabetes in the elderly has a genetic basis.[1] Older people with a family history are often more likely to develop this illness as they age. In genetically susceptible people, various factors may increase the likelihood of type 2 diabetes developing. Elderly patients with diabetes have normal hepatic production of glucose, which is in contrast to younger subjects.[2] In lean elderly subjects, the principal defect appears to be impaired glucose-induced insulin release, whereas in the obese elderly, resistance to insulin-mediated glucose disposal is the major problem.[2]

Multiple drugs, reduced physical activity and a diet with low intake of complex carbohydrates also contribute to this increasing prevalence. Further research into discovering the molecular abnormalities in older people with diabetes is warranted.

Table 101.1 Risk factors for diabetes mellitus in older subjects.

- Aged 65 years and over
- People of Asian, Afro-Caribbean or African origin
- BMI >27 kg m^{-2} and/or large waist circumference
- Those with manifest cardiovascular disease or hypertension with or without hyperlipidaemia
- Presentation with a stroke
- Presentation with recurrent infections
- Use of diabetogenic drugs, e.g. corticosteroids, estrogens
- A family history of diabetes mellitus
- Those with IGT/IFG

Modes of presentation

Diabetes in older people has a varied presentation and may be insidious, which ultimately delays diagnosis[3] (Table 101.2). Detection of diabetes during hospital admissions for other comorbidities or acute illnesses is relatively common, although even when hyperglycaemia has been recognized initially, about half of the subjects receive no further evaluation for diabetes or treatment.[4] Some patients do not have the classic features of either diabetic ketoacidosis or hyperosmolar non-ketotic coma but present with a 'mixed' disturbance of hyperglycaemia (blood glucose levels 15–25 mmol l^{-1}), arterial blood pH of 7.2–7.3 (not particularly acidotic) and without marked dehydration or change in level of consciousness.

Impact of diabetes mellitus

Older patients with diabetes appear to burden the hospital care system two to three times more than the general

Table 101.2 Varying presentation of diabetes in older people.

Asymptomatic (coincidental finding)	
Classical osmotic symptoms	
Metabolic disturbances	Diabetic ketoacidosis
	Hyperosmolar non-ketotic coma
	'Mixed' metabolic disturbance
Spectrum of vague symptoms	Depressed mood
	Apathy
	Mental confusion
Development of 'geriatric' syndromes	Falls or poor mobility: muscle weakness, poor vision, cognitive impairment
	Urinary incontinence
	Unexplained weight loss
	Memory disorder or cognitive impairment
Slow recovery from specific illnesses or increased vulnerability	Impaired recovery from stroke
	Repeated infections
	Poor wound healing

population[5] and use primary care services two to three times more than non-diabetic controls.[6] This latter primary care study from Denmark indicated that insulin-treated patients accounted for more than half of the service provision, mainly due to chronic vascular disease, with a correspondingly high number of hospital clinic visits.

Several UK-based studies have defined the prevalence of elderly patients in hospital diabetic populations. This has ranged from 4.6% (Edinburgh[7]) to 8.4% (Cardiff[8]).

Several important population-based and community studies have revealed that diabetes in older subjects is associated with considerable morbidity, mainly due to the long-term complications of diabetes. These include the Oxford Study,[9] the Poole Study,[10] the Nottingham Community Study[11] and the Welsh Community Diabetes Study.[12] In the last study, in subjects aged 65 years and over, one in three subjects with diabetes had been hospitalized in the previous 12 months (compared with one in six non-diabetic controls). One in four diabetic subjects required assistance with personal care and older people with diabetes had significantly lower levels of health status compared with non-diabetic counterparts. Visual acuity was impaired in 40% of diabetic subjects (compared with 31% of controls) and diabetes was found to be associated with an increased risk of visual impairment {odds ratio (OR) = 1.50 [95% confidence interval (CI) 1.09–2.05]}. Factors that were significantly associated with visual loss in diabetic subjects included advanced age, female gender, history of foot ulceration, duration of diabetes and treatment with insulin.

Diabetic foot disease

A study in The Netherlands[13] identified increasing age and a higher level of amputation as important factors leading to increases in both the period of hospitalization and the associated costs. The 3 year survival following lower extremity amputation is about 50%[14] and in about 70% of cases, amputation is precipitated by foot ulceration.[15] The principal antecedents include peripheral vascular disease, sensorimotor and autonomic neuropathy, limited joint mobility (which impairs the ability of older people to inspect their feet) and high foot pressures.[16]

The majority of the elderly diabetic population is at increased risk of developing foot ulcers and various risk factors have been identified (Table 101.3). Peripheral sensorimotor neuropathy, which is the primary cause or contributory factor in the vast majority of cases, may cause common symptoms of numbness, lancinating and burning pain, 'pins and needles' and hyperesthesia, which is typically worse at night and evidence of high foot pressures leading to gait disturbances, falls and other foot injuries. The presence of visual loss may exacerbate the consequences of this situation.[17]

Table 101.3 Risk factors for foot ulceration in the elderly.

- Peripheral sensorimotor neuropathy
- Automatic neuropathy
- Peripheral vascular disease
- Limited joint mobility
- Foot pressure abnormalities, including deformity
- Previous foot problems
- Visual loss
- History of alcohol abuse

Erectile dysfunction

After the age of 60 years, erectile dysfunction (ED) may affect 55–95% of diabetic men, while the corresponding figure for non-diabetic counterparts is 50%.[18] ED is defined as the inability to attain and maintain an erection satisfactory for sexual intercourse and is a complex problem involving several mechanisms: vasculopathy, autonomic neuropathy, hormonal dysregulation, endothelia dysfunction and psychogenic factors have all been implicated. Drug-related causes may be a particular problem in older patients, with thiazide diuretics, cimetidine, β-blockers and spironolactone especially being implicated. An alcohol history must be looked for. ED is evaluated initially with an interview with the patient and sexual partner where appropriate. A comprehensive history, full medical examination, blood testing for diabetes control, lipids, testosterone and thyroid function tests are necessary. Other more sophisticated tests are available through diabetes ED clinics in most large centres and may involve testing for prolactin, other gonadotrophins and nocturnal penile tumescence. For many older patients, extensive testing is often avoided. Type 5 phosphodiesterase inhibitors appear to be effective for the treatment of erectile dysfunction in carefully selected older people with diabetes.[19,20]

Metabolic comas

Older subjects with diabetes may present with either diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar non-ketotic (HONK) coma. HONK occurs predominantly in subjects aged over 50 years. Compared with the young, older subjects with hyperglycaemic comas have a higher mortality, have a greater length of stay in hospital following admission, are less likely to have had diabetes diagnosed previously, are more likely to have renal impairment and require a greater amount of insulin as treatment.[21]

The tendency for hyperosmolarity in HONK comas may be worsened in elderly people, who may not appreciate thirst well, may have difficulty drinking enough to compensate for their osmotic diuresis and may also be on diuretics. It also appears that hyperosmolarity not only worsens insulin resistance but may also inhibit lipolysis.

Death may be due to the metabolic disturbance and to acute illnesses such as pneumonia and myocardial infarction. The cause of the hyperglycaemia may be infection, infarction, inadequate hypoglycaemic treatment or inappropriate drug treatment. Residents of care homes are also at increased risk of HONK coma associated with appreciable mortality.[22] Thiazide diuretics and steroids are known to increase blood glucose levels and may precipitate DKA; thiazide diuretics and frusemide may be particularly likely to precipitate HONK coma.

Diabetes-related disability, cognitive dysfunction and depression

Diabetes is associated with both functional impairment and disability. The wide spectrum of vascular complications, acute metabolic decompensation, adverse effects of medication and the effects of the condition on nutrition and lifestyle behaviour may all create varying levels of impairment and/or disability. These changes may have adverse rebound effects on vulnerability to other comorbidities, independence and quality of life.

In the 1998 *Health and Retirement Survey* (>6300 subjects aged 51–61 years at baseline), diabetes was identified as an important predictor of failing to recover from a mobility difficulty over a 2-year follow-up period.[23] In a systematic literature review of longitudinal studies examining the relationships between various risk factors and functional status outcomes,[24] diabetes was one of five conditions (others were hypertension, stroke or TIA, arthritis), which reported 10 or more studies showing a significant association between the risk factor and subsequent functional decline.

In a study examining the relationship between various chronic disease states and disability, a survey from Madrid, Spain,[25] of 1001 subjects aged 65 years and over living at home showed that diabetes was one of four chronic diseases (the others were cerebrovascular disease, depression/anxiety disorders) that had a strong association with disability [OR = 2.18 (95% CI, 1.24–3.83)].

The Welsh Community Diabetes Study[12] revealed significant excesses in physical {Barthel activities of daily living (ADL), $p < 0.0001$; extended ADL, $p < 0.0001$; cognitive [Mini Mental State Examination (MMSE)], $p < 0.001$; clock test, $p < 0.001$}, mobility (use of walking aid, $p < 0.01$) and visual disabilities [Snellen visual acuity (VA) chart, $p < 0.01$] in diabetic subjects assessed by objective measures.

In a cross-sectional survey of community-dwelling older Mexican Americans aged 65 years and over ($n = 2873$), the presence of diabetes predicted poorer performance on tests of lower limb function.[26]

The Third National Health and Nutrition Examination Survey (NHANES III) revealed that diabetes was a major cause of physical disability among subjects aged 60 years and over.[27] Disability in at least one of the physical tasks examined was reported in 63% of diabetic women (controls, 42%) and 39% of diabetic men (controls, 25%), with stronger associations between diabetes and more severe forms of disability. Diabetes was shown to have a 2–3-fold increased likelihood of a mobility disorder, with coronary heart disease being a major contributor to this excess disability in both sexes and stroke being an important contributor among men.

Other studies that have examined this relationship include the *Women's Health and Ageing Study* (2002)[28] and the *Study of Osteoporotic Fractures* (2002).[29] In the latter study, in community-dwelling white women aged 65–99 (mean 71.7) years, diabetes was associated with a 42% increased risk of any incident disability and a 53–98% increased risk of disability for specific tasks, for example, walking two to three blocks on level ground or doing housework.

Diabetes in the elderly is associated with an increased risk of falls and fractures.[30,31] This increased risk can be explained by many of factors noted above, including peripheral neuropathy, reduced vision and impaired strength and mobility. Insulin therapy is associated with increased falls. This is probably due in part to more severe disease and/or hypoglycaemic episodes. With regard to the latter, a low A1C in insulin users was associated with an increased risk of falls.[30]

Cognitive dysfunction

A decline in cognitive function has been demonstrated in older subjects with type 2 diabetes.[32] This can be demonstrated using relatively straightforward tests such as the Folstein MMSE[33] or the clock test.[34]

The Zutphen Study (1995)[35] and the Kuopio Study (1998)[36] showed that impaired glucose tolerance (IGT) is linked to cognitive dysfunction and increased serum insulin may be associated with decreased cognitive function and dementia in women. The Rotterdam Study (1996) showed that type 2 diabetes may be associated with both Alzheimer's disease and vascular dementia,[37] and the Rochester Study (1997) demonstrated that the risk of dementia is significantly increased for both men and women with type 2 diabetes.[38] In a 7 year follow-up study (the Hisayama Study, 1995), type 2 diabetes was associated with an increased risk of developing vascular dementia.[39] Poor glucose control may be associated with cognitive impairment that recovers following improvement in glycaemic control.[40] A prospective cohort study involving 682 women with self-reported diabetes (mean age of population sample 72 years) followed up for 6 years indicated a twofold increased risk of cognitive impairment and a 74% increased risk of cognitive decline.[41] Women who had had diabetes for longer than 15 years had a threefold increase of having cognitive impairment at baseline and a doubling of the risk of decline.

Table 101.4 Benefits of early recognition of cognitive impairment in diabetes.

- Prompts the clinician to consider the presence of cerebrovascular disease and to review other vascular risk factors
- May be an early indicator of Alzheimer's disease and provides early access to medication
- Allows patients and families to benefit early with social and financial planning and access to information about support groups and counselling
- Creates opportunities to consider interventions for diabetes-related cognitive impairment: optimizing glucose control; controlling blood pressure and lipids

In the Framingham Study (1997), type 2 diabetes and hypertension were found to be significant but independent risk factors for poor cognitive performance (on tests of visual organization and memory) in a large prospective cohort sample followed for over 20 years.[42] This relationship between cognitive decline and with the presence of either diabetes and hypertension was also observed in the Atherosclerosis Risk in Communities (ARIC) Study (2002) in a 6 year follow-up of nearly 11 000 individuals aged 47–70 years at initial assessment.[43] Hyperinsulinaemia in hypertension has also been shown to be associated with poorer cognitive performance.[44]

Various benefits may accrue from the early recognition of cognitive impairment in older people with diabetes (Table 101.4). Depending on its severity, cognitive dysfunction in older diabetic subjects may have considerable implications, which include increased hospitalization, less ability for self-care, less likelihood of specialist follow-up and increased risk of institutionalization.[45]

Cognitive dysfunction may result in poorer adherence to treatment, worsen glycaemic control due to erratic taking of diet and medication and increase the risk of hypoglycaemia if the patient forgets that they have taken the hypoglycaemic medication and repeat the dose.

Type 2 diabetes mellitus and depression

Diabetes was found to be significantly associated with depression, independent of age, gender or presence of chronic disease in one study;[46] also, the presence of diabetes appears to double the odds of developing depression.[47] The finding of depression was the single most important indicator of subsequent death in a group of diabetic patients admitted into hospital.[48] Failure to recognize depression can be serious since it is a long-term, life-threatening, disabling illness and has a significant impact on quality of life.[49] Depression may be associated with worsening diabetic control[50] and decreased treatment compliance. In the *Baltimore Epidemiological Project* (1996), a 13-year follow-up of more than 3400 household residents (about one in seven was aged 65 years and over), major depressive disorder had an adjusted OR of 2.23 for predicting the onset of type 2 diabetes.[51]

Importance of functional evaluation

Functional evaluation of older people with diabetes mellitus using well-validated assessment tools is an essential step in the initial assessment process. Evaluation of functional status should be a multidisciplinary approach and comprise at least three main areas for measurement: physical, mental and social functioning. However, further evaluation with measures of self-care abilities and independent living skills (generally assessed by ADL tools) are also required. The benefits of functional assessment in the context of diabetes are indicated in Table 101.5.

Functional assessment is a primary component of comprehensive geriatric assessment (CGA), which is an essential methodology for geriatric medical practice.[52] CGA is crucial at the initial assessment and helpful in planning care and rehabilitation and monitoring progress. CGA can be performed in many clinical and healthcare locations and not only involves a basic assessment of functional status but also includes various limited screening techniques, evaluation of social and medical problems, instigating initial treatment and ensuring follow-up. CGA and its variants (including in-home assessment packages) have been demonstrated to reduce mortality (by 14% at 12 months), increase the chance of remaining at home after referral (26% at 12 months), reduce hospital admissions (12% at 12 months), with gains in cognition and physical function having also been observed.[53] Not all patients gain from this approach and targeting is required. Criteria for older subjects with type 2 diabetes who may derive benefit from comprehensive assessment methods with a measure of functional status are given in Table 101.6. A summary of the various assessment methods in common use is given elsewhere in this book. The authors do not advocate that all practitioners in Europe should adopt CGA as a routine part of their assessment processes, but suggest that functional assessment become a routine measure in older

Table 101.5 Benefits of functional assessment: diabetes-related.

- Measures ability to comply with treatment goals and adherence to nutritional advice
- Assesses self-care ability and ability to apply sick-day rules
- Assesses the impact of vascular complications of diabetes, e.g. peripheral vascular disease or neuropathy
- Assesses likely ability to gain from educational interventions
- Assesses need for carer support
- Identifies any quality-of-life issues related to the disease or its treatment

Table 101.6 Criteria for targeting patients with type 2 diabetes for comprehensive geriatric assessment.

- Presence of a 'geriatric syndrome': confusional state, depression, falls, incontinence, immobility, pressure sores
- Those with several coexisting morbidities apart from diabetes with complex drug regimens
- Those with disabilities due to lower limb vascular disease or neuropathy requiring a rehabilitation programme
- Absence of a terminal illness or dementing syndrome

people with type 2 diabetes at diagnosis and at regular intervals thereafter.

Treatment and care issues: learning from the literature

The major aims in the management of older people with type 2 diabetes involve both medical and patient-oriented factors (Table 101.7). An initial plan for the early evaluation of patients is reflected in Table 101.8, which should form a framework for instigating the appropriate treatment pathway. An important aim of risk assessment in the general population is to identify subclinical cardiovascular risk, which may be the principal cause of undetected functional impairment or frailty in older people. Coronary risk charts are often based on Framingham data[54,55] and can be used to identify either 5 or 10 year event rates, but it is important to note that cardiovascular risk data are generally based on populations of individuals up to a maximum age of 74 years only. In a large proportion of older people with type 2 diabetes, excess cardiovascular risk is evident and active intervention should be considered.

A summary of the therapeutic areas for intervention and the relevant evidence base is provided in Table 101.9 and

Table 101.7 Major aims in managing older people with diabetes.

Medical	Patient-oriented
Freedom from hyperglycaemic symptoms	Maintain general wellbeing and good quality of life
Prevent undesirable weight loss	Acquire skills and knowledge to adapt to lifestyle changes
Avoid hypoglycaemia and other adverse drug reactions	Encourage diabetes self-care
Estimate cardiovascular risk as part of screening for and preventing vascular complications	
Detect cognitive impairment and depression at an early stage	
Achieve a normal life expectancy for patients where possible	

Table 101.8 Care plan for initial management of diabetes in an elderly person.

- Establish realistic glycaemic and blood pressure targets
- Ensure consensus with patient, spouse or family, general practitioner, informal carer, community nurse or hospital specialist
- Define the frequency and nature of diabetes follow-up
- Organize glycaemic monitoring by patient or carer
- Refer to social or community services as necessary
- Provide advice on stopping smoking, increasing exercise and decreasing alcohol intake

the main types of insulin regimes employed are indicated in Table 101.10. In the UK, the licence for pioglitazone has recently been modified to allow 'triple' therapy (pioglitazone and both a sulfonylurea and metformin to be coprescribed).

Glucose regulation

The management of blood glucose must form part of a multifaceted approach to dealing with the metabolic disorder of type 2 diabetes in older people since most patients have evidence of other cardiovascular risk factors and at least half are likely to satisfy the criteria for the metabolic syndrome proposed by a WHO Expert Committee in 1998[56] and more recently by the International Diabetes Federation.[57]

Although there is now overwhelming evidence that the level and duration of glycaemia influence the development of diabetes-related complications, specific studies in older subjects (>70 years) with type 2 diabetes are lacking.

The majority of the studies conducted in older populations have involved patients of Caucasian ancestry affected by type 2 diabetes. The applicability of these results to the elderly type 1 diabetic patient or to the non-Caucasian type 2 diabetic patient remains to be assessed. However, no randomized controlled trials assessing the impact of achieving optimal glucose control on primary prevention of cardiovascular outcomes in the elderly diabetic patient are available.

Recommendations

The following represent some of the more important recommendations on glucose regulation taken from the European Guidelines (Executive Summary, European Diabetes Working Party for Older People, 2011):[58]

1 At initial assessment, all patients with type 2 diabetes aged less than 85 years should have a cardiovascular-risk assessment. Evidence level 1+; Grade of recommendation A.

2 For older patients with type 2 diabetes, with single system involvement (free of other major comorbidities), a target HbA1c (DCCT aligned) range of 7.0–7.5% and a fasting glucose range of 6.5–7.5 mmol l^{-1} should be aimed for. Evidence level 2++; Grade of recommendation B.

Table 101.9 Treatment targets and intervention studies for elderly diabetic patients.

Blood glucose level	Blood pressure	Blood lipid level	Aspirin use
No specific studies in older people with diabetes	A 10 mmHg (systolic) and 5 mmHg (diastolic) fall in blood pressure in the intensive group resulted in a 24% decrease in risk of any diabetes-related endpoint, 44% reduction in risk of stroke and 37% risk reduction in macrovascular disease	Few studies in older people with diabetes	Antiplatelet Trialists Collaboration: 75–325 mg per day reduced major cardiovascular events in high-risk patients by 25%; NNT 26 (17–66)
UKPDS: HbA1c <7%; fasting blood glucose <7 mmol l^{-1}	HOT Study: diastolic lowering to ≤83 mmHg	PROSPER: pravastatin for 3.2 years resulted in a 1.0 mmol l^{-1} fall in LDL cholesterol and a modest relative risk (RR) of 15% for the primary composite outcome; no change in the decline of cognition was seen	HOT Study: 75 mg per day reduced major cardiovascular events by 15% and myocardial infarction by 36%; stroke was unaffected
A reduction in HbA1c of 0.9% between the study groups resulted in a 12% reduction in risk of any diabetes-related endpoint, but no significant reduction in major cardiovascular events	A systolic BP<80 mmHg resulted in a 51% reduction in major cardiovascular events compared with the target group of ≤90 mmHg		
	SHEP Study: systolic BP <150 mmHg A 34% reduction in risk of cardiovascular disease in the actively treated group was observed	Heart Protection Study: treatment with simvastatin for 5 years resulted in a fall of 1.0 mmol l^{-1} of HDL cholesterol and a 25% RR in incidence of first nonfatal or fatal stroke	
	A fall of 23/7 mmHg in the actively treated group was associated with a 55% decrease in mortality and a 69% reduction in cardiovascular endpoints MICRO-HOPE was not target driven but showed highly significant reductions in cardiovascular risk with ramipril for 4.5 years (22% RR in myocardial infarction; 33% RR in stroke). LIFE study: 24% RR in primary composite endpoint of cardiovascular mortality, stroke and all myocardial infarction after minimum 4 years of losartan treatment compared with atenolol. ALLHAT showed that after a mean of 4.9 years of follow-up, there were no significant differences in outcome between chlorthalidone, lisinopril or amlodipine	LIPID, CARE, 4S, VA-HIT Studies: total cholesterol <5 mmol l^{-1}, HDL cholesterol >1.0 mmol l^{-1} Triglycerides <2.0 mmol l^{-1} ALLHAT-LLT: 4.9 years of pravastatin showed modest reductions in cholesterol only and did not reduce mortality or coronary heart disease	
		ASCOT-LLA: study stopped after 3.3 years showing highly significant benefits of atorvastatin; a fall of 1.0 mmol l^{-1} of HDL cholesterol gave a 36% RR of primary end point but subgroup analysis of diabetic patients showed no benefit	

Table 101.10 Practice-orientated guidelines for insulin treatment in older people.

Treatment	Indications	Advantages	Disadvantages
Once-daily insulin	Frail subjects Very old (>80 years) Symptomatic control	Single injection Can be given by carer or district nurse	Control usually poor Hypoglycaemia common
Twice-daily insulin	Preferred if good glycaemic control Suitable for type 1 diabetes	Low risk of hypoglycaemia Easily managed by most older diabetic people	Normoglycaemia difficult to achieve Fixed meal times reduce flexibility Expensive
Basal/bolus insulin	Well-motivated individuals Can reduce microvascular complications	Allows tight control For acute illness in hospital Flexible meal times	Frequent monitoring required to avoid hypoglycaemia
Insulin plus oral agents	If glycaemic control is unsatisfactory with oral agents alone To limit weight gain in obese subjects	Limits weight gain by reducing total daily insulin Increased flexibility	May delay conversion to insulin in thin or type 1 patients

3 For frail (dependent; multisystem disease; care home residency including those with dementia) patients where the hypoglycaemia risk is high and symptom control and avoidance of metabolic decompensation are paramount, the target HbA1c range should be 7.6–8.5% and the fasting glucose range 7.0–9.0 mmol l^{-1}. Level of evidence 1+; Grade of recommendation A.

4 Glibenclamide should be avoided for newly diagnosed cases of type 2 diabetes in older adults (aged >70 years) because of the marked risk of hypoglycaemia. Level of evidence 1+; Grade of recommendation A.

5 In older adults with diabetes, the use of premixed insulin and prefilled insulin pens may lead to a reduction in dosage errors and an improvement in glycaemic control. Level of evidence 2++; Grade of recommendation B. *More recent data suggest that the clock test may be used to predict which elderly patients are likely to have trouble with insulin therapy.*[59] *Newer insulins such as glargine and insulin detemir may be associated with a lower frequency of hypoglycaemia than conventional insulin therapy in the elderly*[60,61] *and should be considered when problems arise with conventional insulin therapy.*

6 Where the risk of hypoglycaemia is considered moderate (renal impairment, recent hospital admission) to high (previous history, frail patient with multiple comorbidities, resident of a care home) and a sulfonylurea is considered, use an agent with a lower hypoglycaemic potential, for example, a DDP4 inhibitor, lower risk sulfonylurea. *Risk of hypoglycaemia: glibenclamide > glimepiride > gliclazide > tolbutamide.*[62] *Meglitinides are associated with a lower frequency of hypoglycaemia in the elderly than glyburide and may be preferred in subjects with irregular eating habits.*[63,64]

The thiazolidenediones pioglitazone and rosiglitazone are effective agents in the elderly, but the adverse cardiovascular effects reported with rosiglitazone use have led to its recent withdrawal in the European Union. Unfortunately, the incidence of fluid retention is greater in elderly patients treated with these drugs and concerns have been raised about an increased risk of fractures in elderly women and, potentially, an increased risk of cardiac events with rosiglitazone.[65–67]

It has been recognized for several years that the insulin response to oral glucose is greater than that to intravenous glucose, a phenomenon known as the incretin effect. The hormones responsible for this effect are GIP and GLP-1. Although patients with diabetes do not respond to GIP, the ability of GLP-1 to stimulate insulin secretion is preserved. Recently, drugs that act on the incretin pathway have attracted increasing interest because they do not cause weight gain and may even stimulate weight loss, rarely cause hypoglycaemia and suppress the high glucagon levels that are often seen in patients with diabetes. We have shown that GLP-1 is a very effective agent in elderly patients, but it is impractical for long-term use because it must be given by continuous infusion. The long-acting analogues of GLP-1, liraglutide and exenatide, have not yet been studied in the elderly. GLP-1 is broken down rapidly in the circulation by the enzyme DPPIV and inhibitors of this enzyme have recently been released for clinical use. Recent studies in the elderly have shown that these drugs can be very effective in this age group[68,69] and appear to safe. However, early reports have suggested that incretin analogues may be associated with an increased risk of pancreatitis. In addition, because DPPIV is a ubiquitous enzyme, especially in the immune system, concern has been raised about potential impacts on the risk of infection and cancer. For this reason, these drugs should be used with caution until more post-marketing surveillance has been conducted.

7 Optimal glucose regulation may help maintain cognitive performance, improve learning and memory and may help to minimize symptoms of mood disorder in

patients with depression. Level of evidence 1+; Grade of recommendation A.

Glucose targets

Four recent studies have had a major impact on our thinking about the benefits of tight glycaemic control. The ACCORD, ADVANCE and VADT studies[70–72] all evaluated the impact of tight glycaemic control on patients with a mean age in the 60s, many of whom were over 70 years of age. All patients had a diabetes duration of at least 5 years and at least one-third had evidence of complications at the outset of the study. The studies found no impact of tight glycaemic control on the risk of macrovascular events, but a potential impact on microvascular events. In the ACCORD study, the risk of death appeared to be increased in the group randomized to tight glycaemic control. The follow-up study of the UKPDS,[73] however, found that after 10 years, the benefits of glycaemic control on microvascular events persisted and a positive impact on macrovascular events and overall mortality became apparent. It is worth noting that patients in this study had new-onset diabetes, were substantially younger and were free from complications at the study onset. The results of these studies have been hotly debated. The consensus of opinion is that if a patient has new-onset diabetes and is free from complications, every effort should be made to control blood sugar rigorously. For patients with a longer duration of diabetes who have complications, glycaemic targets should be more modest and more emphasis should be placed on control of blood pressure and lipids.

Inpatient diabetes care

Early studies of critically ill patients suggested that tight control of blood sugar reduced mortality and improved other important outcomes.[74,75] However, more recent information suggests that tight control may do more harm than good[76,77] and experts are recommending that a glucose level of 7–10 mmol l^{-1} is an appropriate target in an intensive care setting. To date, there have been no studies evaluating the benefits or risks of tight glycaemic control for elderly inpatients outside the intensive care setting. Based on the concerns raised above, it would seem prudent to target preprandial sugars in the range 7–10 mmol l^{-1} in these patients pending the outcome of further studies.

Blood pressure regulation

Adverse cardiovascular outcomes (stroke and coronary heart disease) are clearly and directly related to increasing levels of blood pressure. In non-diabetic individuals, this is more pronounced in men than in women; antihypertensive treatment has been shown to produce worthwhile reductions in risk, especially in high-risk patients such as those with diabetes or the elderly, where the absolute benefit is greater.

Increasing age is also an independent risk factor for cardiovascular disease even in low-risk individuals with normal blood pressure.

There is an age-related increase in systolic blood pressure but diastolic blood pressure tends to peak at 66–69 years of age and then falls. A large percentage of older patients will have isolated systolic hypertension where the diastolic blood pressure is not raised. Hypertension is also associated with the insulin resistance syndrome in older subjects and in diabetic subjects who develop microalbuminuria, thus increasing the risk of nephropathy and end-stage renal failure.

Diagnosis of hypertension in diabetes

Established hypertension exists when blood pressure readings are persistently above 140/90 mmHg (Korotkov IV) over at least 1 month or when the diastolic blood pressure exceeds 110 mmHg or when there is evidence of target organ damage. As the presence of diabetes imposes a greater cardiovascular risk, it is reasonable to have lower blood pressure thresholds for treatment in these subjects, but most guidelines indicate 140/90 mmHg as the treatment threshold with lower target values for those with diabetes. Four national/international sets of guidelines for hypertension have been published and these can be downloaded from the relevant website or author address, for example, http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf. Each major guideline has a section on the management of hypertension in diabetes, but age modification of targets and thresholds is not detailed. In addition, there have been no specific randomized controlled trials in older subjects with type 2 diabetes and hypertension that have directly investigated the benefits and outcomes of treating blood pressure to target.

On the basis of an analysis of these sets of guidelines and the relevant clinical evidence base, the European Diabetes Working Party for Older People has developed an updated Executive Summary[58] of their 2004 guideline[78] and have set targets described in the clinical recommendations below.

Recommendations

1 The threshold for treatment of high blood pressure in older subjects with type 2 diabetes should be 140/80 mmHg or higher present for more than 3 months and measured on at least three separate occasions during a period of lifestyle management advice (behavioural: exercise, weight reduction, smoking advice, nutrition/dietary advice). Level of evidence 2++; Grade of recommendation B. *This decision is based on the likelihood of reducing cardiovascular risk in older subjects balanced with issues relating to tolerability, clinical*

factors and disease severity and targets likely to be achievable with monotherapy and/or combination therapy and with agreement with primary care colleagues. As most subjects aged 70 years and over with type 2 diabetes and hypertension will already by definition have a high CV risk, no additional weighting for extent of CV risk has been applied. A lower value of blood pressure should be aimed for in those who are able to tolerate the therapy and self-manage, and/or those with concomitant renal disease.

2 For frail (dependent; multisystem disease; care home residency including those with dementia) patients, where avoidance of heart failure and stroke may be of greater relative importance than microvascular disease, an acceptable blood pressure is <150/<90 mmHg. Evidence level 2+; Grade of recommendation C – extrapolated data.

3 Optimal blood pressure regulation should be aimed for to help maintain cognitive performance and improve learning and memory – *Good Clinical Practice point*.

Guidelines on specific treatment strategy and medication

4 In older patients with a sustained blood pressure (≥140/80 mmHg) and in whom diabetic renal disease is absent, first-line therapies can include use of ACE inhibitors, angiotensin II receptor antagonists, long-acting calcium channel blockers or thiazide diuretics. Level of evidence 1+; Grade of recommendation A. *In terms of comparable efficacy, safety and cost-effectiveness, treatment with a thiazide diuretic may be preferred as the first-line therapy. Short-acting calcium channel blockers should not be used. β-Blockers are useful for patients with previous myocardial infarction, but are not particularly effective for the treatment of hypertension in the elderly patient with diabetes*.

The choice of antihypertensive agent should take into account metabolic factors, the presence or not of renal impairment or cardiovascular disease and the likelihood of causing postural hypotension, which may have particularly adverse consequences in older subjects. At the present time, α-adrenoreceptor blockers have no special indications in the treatment of hypertension in diabetes and may be harmful. The use of low-dose fixed combinations of two agents such as a thiazide diuretic plus an ACE inhibitor may also have additional advantages.

5 In older patients with a sustained blood pressure (≥140/80 mmHg) with microalbuminuria or proteinuria, treatment with an ACE inhibitor is recommended. Level of evidence 1+; Grade of recommendation B. *An angiotensin II receptor antagonist may be considered as an alternative to an ACE inhibitor where the latter class of drug is not tolerated or is contraindicated*.

Lipid regulation

Coronary heart disease (CHD) is the most common cause of mortality in type 2 diabetes and remains the principal challenge for older people with this metabolic disorder. Elevated levels of blood lipids are an independent risk factor for CHD and there is published evidence of cardiovascular benefit in using a lipid-lowering regimen, although this is limited in older subjects. As part of a multifaceted approach to the metabolic consequences of diabetes, effective management of blood lipids is essential to optimize vascular outcomes. Attention to risk factors such as smoking and other metabolic derangements such as blood pressure is also of paramount importance.

Cardiovascular risk assessment

Categories of risk based on lipoprotein levels in adults with diabetes mellitus according to most international recommendations are given without modification concerning age and duration of diabetes. Since general cardiovascular risk is increasing with both variables, especially age, cardiovascular risk in older diabetic patients is generally underestimated according to non-age-specific risk assessment. One approach is to calculate global risk in individuals without overt cardiovascular disease (primary prevention) using the Framingham Heart Study equation or the WHOISH risk table.[79,80] Another method relies on the calculation of individual risk on the basis of epidemiological data. For the purposes of this chapter, 'high' and 'low' cardiovascular risks are as described in Table 101.11.

Several large-scale clinical trials have shown benefit with statin therapy of high-risk (cardiovascular risk) individuals and these included a proportion of older subjects. They have also demonstrated that these agents are well tolerated and safe, with no consistent additional risk of cancer or non-vascular morbidity or mortality. Previous statin trials indicate that the absolute reduction in LDL cholesterol produces similar proportional risk reductions in older and younger people.

Table 101.11 High and low 10 year cardiovascular risk definitions.

High risk
Has manifest cardiovascular disease (history of symptoms of coronary heart disease, stroke or peripheral vascular disease) or a coronary (Risk Assessment Chart)[a] event risk of >15%;
Low risk
Does not manifest cardiovascular disease and whose coronary event risk[a] is ≤15%

[a]On the basis of joint British recommendations: British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society and British Diabetic Association. Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. *BMJ* 2000;**320**:705–8. Adapted from NICE (UK).

Target values for total cholesterol and LDL cholesterol

Target values for treatment decisions based on total/LDL cholesterol level in adults with diabetes should be adopted without age limitation, especially in otherwise healthy and independent individuals ('single disease model'). Categories of risk are available depending on lipid levels (*American Diabetes Association criteria*), although treatment decisions based on an estimation of a 10 year cardiovascular risk may also be used (*National Institute for Health and Clinical Excellence* (*NICE*) guidelines]. Additional measurement of HDL cholesterol provides a more accurate assessment of cardiovascular risk because of the inverse relationship between cardiovascular risk and HDL cholesterol. These recommendations may not be directly applicable for old (>75 years of age) and very old (>85 years of age) patients because of the presence of multiple comorbidities, high dependency levels, care home residency and/or end-stage dementia ('frailty model').[81] In these situations, limited life expectancy or competing non-cardiovascular causes of mortality (e.g. cancer or infections), may mask or remove any benefit from lipid lowering and increase the likelihood of adverse drug reactions. Lipid regulation on an individual basis is required.

Initial assessment of the older patient

Initial assessment should include enquiry about alcohol consumption and presence or not of renal, thyroid or liver disease. An estimate of the level of physical activity is important and overweight (and obese) subjects should be encouraged to lose weight and be given exercise advice relative to their capability and overall functional status. Dietary modification may be of benefit as part of a revised lifestyle plan.

Assessments of total, HDL and LDL cholesterol and triglycerides are usually required as part of the annual review process (Grade of recommendation C) and should preferably be fasting samples at the start of treatment for those with abnormal profiles.

For these *Guidelines*, an abnormal lipid profile in older subjects can be regarded as total cholesterol $\geq 5.0\,mmol\,l^{-1}$, LDL cholesterol $\geq 3.0\,mmol\,l^{-1}$ or triglycerides $\geq 2.3\,mmol\,l^{-1}$.

In general, pharmacological therapy of abnormal lipid levels should not be delayed or ignored because of the age of the individual and should be regarded as part of the routine interventions in managing older people with diabetes. In patients prescribed a statin, the clinician must always be alert to the potential side effects of treatment, including reversible myositis and myopathy.

Recommendations

Some of the principal recommendations related to the use of statins and fibrates in older people with diabetes can be summarized as follows:

1 Statin therapy is well tolerated and can be safely used in older subjects with diabetes.

2 Primary prevention: in subjects with no history of cardiovascular disease, a statin should be offered to patients with an abnormal lipid profile if their 10-year cardiovascular risk is >15%. *There is little evidence at present for primary preventative strategies for subjects aged >80 years*.

3 Secondary prevention: a statin should be offered to patients with an abnormal lipid profile who have proven cardiovascular disease.

4 A fibrate should be considered in patients with an abnormal lipid profile who have been treated with a statin for at least 6 months but in whom the triglyceride level remains elevated ($\geq 2.3\,mmol\,l^{-1}$).

5 A fibrate should be considered in patients with proven cardiovascular disease who have isolated high triglyceride levels ($\geq 2.3\,mmol\,l^{-1}$).

6 For patients with cardiovascular disease who have persistent raised fasting triglycerides $>10\,mmol\,l^{-1}$, referral to a specialist lipid or diabetes clinic is recommended.

Care home diabetes

Within the European Union, the structure and provision of diabetes care within residential care homes are highly variable. High-quality diabetes care is unlikely to be present in the majority of care homes with many underlying reasons accounting for this rather dismal situation. These include organizational difficulties within the institutions, lack of clarity relating to medical and nursing roles and responsibilities, funding issues and a lack of a coherent professional framework for delivering diabetes care.

Several deficiencies of diabetes care within institutional settings have been identified (see Table 101.12). They represent a series of concerns that highlight the need for standards of diabetes care to be established.

A UK study highlighted problems in diabetes care delivery.[82] This study involved a medical examination of and semistructured interview with residents with

Table 101.12 Concerns and deficiencies in diabetes care – institutional facilities.

- Increasing number of institutionalized diabetic elderly
- Lack of specialist medical follow-up
- Inadequate dietary care and lack of structured health professional input
- Lack of individualized diabetes care plans
- Lack of educational and training programmes for care home staff
- No major intervention studies assessing the benefits of metabolic control and/or educational strategies
- Few national standards of diabetes care

diabetes in long-term care facilities in South Wales, which revealed a prevalence of known diabetes of 7.2%. One-third of residents with diabetes tested had a HbA1c >11.0%, 40% of those on oral hypoglycaemic agents were taking the long-acting sulfonylureas chlorpropamide or glibenclamide and none of the homes had a policy in place for recording hypoglycaemic events. Only eight out of 109 diabetic residents had a specialist follow-up arranged. Other health professional input was minimal.

More recently, a retrospective, cross-sectional study using the SAGE (Systematic Assessment of Geriatric Drug Use via Epidemiology) database reported that 47% of residents with diabetes were receiving no antidiabetic medication and that the presence of advanced age, being black, having a low ADL score, cognitive impairment and a low body mass index (BMI) (<21) increased the likelihood of not receiving antidiabetic medication.[83]

These and other studies indicate that diabetic residents of care homes appear to be a highly vulnerable and neglected group, characterized by a high prevalence of macrovascular complications, marked susceptibility to infections (especially skin and urinary tract), increased hospitalization rates and high levels of physical and cognitive disability. Communication difficulties (because of dementia and/or stroke) lead to unmet care needs and lack of self-care abilities and water and electrolyte disturbances increase the risk of metabolic decompensation. Many elderly residents in these institutions are treated with neuroleptic agents, which can have a major impact on patients with impaired glucose tolerance and diabetes,[84] and it is important to consider this fact when evaluating these patients.

Prevalence of diabetes mellitus in care homes

A number of prevalence surveys of diabetes within care homes provide estimates of between 7.2 and 26.7%, depending on the method used for identifying those with diabetes.

Additional information from the population-based SAGE database in the USA,[83] which involves five States and evaluation of all residents using the 350-item minimum data set (MDS), revealed a prevalence of diabetes of 18.1%, which decreased as age increased (e.g. 27% in those aged 65–74 years compared with 13% in those aged 85 years and over). The highest prevalence was recorded in Hispanics (28%) and black non-Hispanics (26%).

In a study screening care home residents for diabetes using two-point (fasting and 2 h postglucose challenge values) oral glucose tolerance tests, the overall prevalence rate (newly diagnosed + known diabetes) was calculated as 26.7%, with a rate of 30.2% for impaired glucose tolerance.[85] The majority of diagnoses were made according to the 2 h values rather than the fasting glucose levels, but it may be argued that these residents are at greater cardiovascular risk and may benefit from an intervention.

Intervention studies in care homes

Few intervention studies of diabetic residents of care homes have been reported. In Denver, CO, an educationally based intervention study in 29 nursing homes consisted of providing workshops and follow-up consultations to administrative staff designed to assist in developing and implementing diabetes care policies and procedures.[86] By 1 year, a significant increase in the adherence to previously published diabetes care plans was observed and although hospital admission rates had not changed, total bed days were smaller. Affiliation to a university-based academic faculty may also lead to an improvement in outcomes for nursing home residents with diabetes. In a study in California, significantly better glycaemic control was observed in a small group ($n = 47$) of nursing home diabetic residents (mean age 81 years; HbA1 8.9% on oral agents) compared with a group of ambulatory diabetic residents (mean age 66 years; 11.8% on oral agents), with only a small number of associated hypoglycaemic events.[87]

A small study (18 subjects) in Stanford, CA,[88] demonstrated that residents of care homes who are in good health and in good glycaemic control (mean fasting glucose of 7 mmol l^{-1}), that the introduction of a 'regular diet' compared with the standard 'diabetes diet' had minimal effects on glucose control, lipid levels and body weight over a 16 week period. In a small study of Italian nursing home residents with diabetes ($n = 30$; mean age 77 years), the substitution with insulin lispro treatment for 4 months as part of a series of treatment periods using regular insulin led to a significant decrease in mean daily blood glucose, HbA1c [7.6 versus 8.5% (regular), $p < 0.01$] and hypoglycaemic episodes.[89]

More recently, in an academic nursing home facility, a 5 month educational programme on dyslipidaemia treatment aimed at physicians and nurse practitioners led to an improvement in the frequency of prescribing lipid-lowering therapy.[90] This New York-based study demonstrated an increase from 26 to 67% for diabetic residents.

Rationale for early detection of diabetes mellitus in care homes

In view of the absence of clinical trial data, the rationale for early detection of diabetes mellitus has not been justified. However, each resident has a right to active investigation and intervention (where appropriate) and it is feasible that several benefits may accrue from such a policy (Table 101.13).

Aims of care for diabetic residents

Residents with diabetes in care homes should receive a level of comprehensive diabetes care commensurate with their health and social needs. The two most important

Table 101.13 Importance of early detection of diabetes mellitus in care homes.

- Improved metabolic control may improve cognition, decrease the risk of hyperosmolar coma and lessen osmotic symptoms
- Earlier treatment may delay vascular complications and reduce disability
- Knowledge of diagnosis of diabetes prompts the physician to be alert to diabetes-related complications, e.g. hyperosmolar coma
- Earlier dietary intervention may delay treatment (and therefore limit adverse drug reactions) with oral agents
- Treatment can reduce symptoms and may increase quality of life and functional wellbeing

aims of care according to the European Guidelines[78] (European Diabetes Working Party for Older People, 2001–2004) are as follows:

1 To maintain the highest degree of quality of life and wellbeing without subjecting residents to unnecessary and inappropriate medical and therapeutic interventions.

2 To provide support and opportunity to enable residents to manage their own diabetes condition where this is a feasible and worthwhile option.

Other crucial objectives of care include: (3) achieving a satisfactory (but optimal) level of metabolic control that reduces both hyperglycaemic lethargy and hypoglycaemia and allows the greatest level of physical and cognitive function; (4) optimizing foot care and visual health that promotes an increased level of mobility, reduced risk of falls and prevents unnecessary hospital admissions; (5) to provide a well-balanced nutritional and dietetic plan that prevents weight loss and maintains nutritional wellbeing; and (6) to screen effectively for diabetic complications regularly, especially eye disease, peripheral neuropathy and peripheral vascular disease that predispose to foot infection and ulceration.

Diabetes care home provision – modern approaches

Several important strategies to improve the quality and outcomes of diabetes care within these settings have been proposed[91] and more recently Diabetes UK has launched national guidance in this area. A series of recommendations have previously been proposed by the European Diabetes Working Party on Older People, as follows.

Recommendations

1 At the time of admission to a care home, each resident requires to be screened for the presence of diabetes.

2 Each resident with diabetes should have an individualized diabetes care plan with the following minimum details: dietary plan, medication list, glycaemic targets, weight and nursing plan.

3 Each resident with diabetes should have an annual review where the medical component is undertaken either by a general practitioner, geriatrician or hospital diabetes specialist.

4 If required, each resident with diabetes should have reasonable access to the following specialist services: podiatry, optometric services, hospital diabetes foot clinic, dietetic services and diabetes specialist nurse.

5 Each care home with diabetes residents should have an agreed Diabetes Care Policy or Protocol that is regularly audited.

Prevention

Impaired glucose tolerance occurs in ~25% of elderly patients and is a precursor for diabetes. The Diabetes Prevention Program showed that although metformin was not effective in the elderly, lifestyle interventions were beneficial in reducing the incidence of diabetes.[92] The Study To Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM)[93] showed than α-glucosidase inhibitors reduced the incidence of diabetes and macrovascular events in elderly patients with impaired glucose tolerance. The DREAM study[94] demonstrated that rosiglitazone is also very effective in the prevention of diabetes in elderly subjects, but this agent has now been withdrawn from the European Union.

Conclusion

Diabetes mellitus in older subjects represents an often complex interplay between ageing, functional loss, vascular disease and the metabolic syndrome. Type 2 diabetes may be a potent cause of both premature and unsuccessful ageing. Functional assessment and estimation of disability levels form part of the important screening process in older adults with diabetes. There is increasing evidence that improving metabolic control will have important benefits even in older subjects. The recently published European Guidelines on managing older people with type 2 diabetes represents an important step forward in the provision of clinical guidance of this often neglected but highly prevalent group. We should encourage more research by randomized controlled design studies that examine the benefits of metabolic intervention and explore the value and cost-effectiveness of different diabetes care models for managing the frail elderly diabetic subject.

Key points

- Diabetes mellitus has a high prevalence in ageing populations and is associated with specific metabolic alterations.

- Cardiovascular disease is a major cause of morbidity and premature disability in older subjects with type 2 diabetes.
- Functional impairment remains a major challenge for clinicians managing older people with diabetes and a working knowledge of assessment methodology is helpful in planning therapies.
- Cognitive dysfunction, depressive illness and falls are important complications and strategies to prevent them require being included in the overall management plan.
- Further research (both basic science and clinical) into the pathogenesis and treatment of type 2 diabetes in senior citizens is urgently required.

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CHAPTER 102

New therapies for diabetes mellitus

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Why do we need new antiglycaemic medications and the 'diabetes conundrum'?

Everyone will agree that elevated blood glucose is bad, but why has it been so difficult to show that lowering blood glucose to normal is good? We have not had the same problem showing that lowering elevated levels of blood pressure and low-density lipoprotein (LDL) are beneficial. Hyperglycaemia leads to increases in mortality and cardiovascular disease, but antiglycaemic therapies have not alleviated this excess burden of disease. This is the 'diabetic conundrum' and it creates opportunities for new antiglycaemic therapies since the old ones have been lacking.

The purpose of this chapter is to discuss and evaluate new glucose-lowering (antiglycaemic) therapies for type 2 diabetes mellitus (T2DM). Although blood pressure- and LDL-lowering therapies are effective and important diabetic therapies, they will not be included in this discussion.

Definition of type 2 diabetes mellitus: disease or risk factor?

The American Diabetes Association (ADA) definition is a good place to start the discussion: *'Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.'* Three points in this definition require emphasis, outlined below.[1]

'Hyperglycaemia', and when does T2DM start?

The difficulty in understanding T2DM is deciding where normoglycaemia leaves off and hyperglycaemia begins. The glycaemic risk for complications probably begins before the glucose level meets the current diagnostic threshold of T2DM. In this sense, hyperglycaemia is more like a risk factor with a continuous rather than dichotomous (i.e. the presence or absence of T2DM) threat to health.

That the therapeutic implications of hyperglycaemia present a graded rather than a dichotomous risk is emphasized by the new AACE treatment algorithm.[2] The AACE therapeutic approach emphasizes that increasing levels of hyperglycaemia require graded intensities of treatment. They divide hyperglycaemia into three tiers, recommending monotherapy for the first tier, duotherapy for the second tier and more complex strategies or consideration of insulin for the third tier. This tiered approach is similar to step therapy for different stages of hypertension in the JNC guidelines. In contrast, the ADA does not consider gradations of hyperglycaemia, but instead recommends a stepwise approach to intensification of therapy in T2DM.[3] The theoretical downside of ADA's stepwise versus AACE's tiered approach is the delay in reaching the desired glycaemic target.

'Defects in insulin secretion and action'

Halting the progression of these defects and worsening hyperglycaemia is one of the major therapeutic challenges in T2DM. With time, therapy must be intensified in both dose and numbers of medications to offset the steady decline in insulin secretion. One strategy is to use insulin sensitizers; another is to find drugs this increase β-cell function or mass or decrease apoptosis. Newer therapies with these characteristics will be reviewed.

'Long-term damage, dysfunction and failure of various organs'

Ultimately, it is the complications that we are most concerned about. They can be divided into microvascular, which responds well to antiglycaemic therapy, and macrovascular, for which it has been harder to show benefit.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Microvascular complications

Small-vessel disease in T2DM is responsible for blindness (retinopathy), renal failure (nephropathy) and lower limb amputations (neuropathy). Glucose-lowering therapy has been proved to reduce these complications (DCCT trial).

Macrovascular complications

Large-vessel disease includes coronary artery, cerebrovascular and peripheral vascular disease. All of the major antiglycaemic trials have failed to show benefits in large vessel disease or mortality in T2DM (ACCORD,[4] ADVANCE,[5] VADT,[6] UKPDS trials).

Cancer complications

Less well appreciated is the association of T2DM and cancer. T2DM patients have approximately twofold higher rates of cancer for a variety of organs, including liver, pancreas, endometrium, breast, colon and bladder, and non-Hodgkin's lymphoma. Potential explanations include the mitogenic effects of insulin (endogenous and exogenous) and underlying metabolic abnormalities such as increased oxidative stress, hyperglycaemia, hyperlipidaemia and obesity. Little is known about the impact of antiglycaemics and cancer, but metformin shows lower cancer rates than insulin and sulfonylurea (SU) therapies.[7]

Current adjunctive therapies for T2DM

Adjunctive therapy

The main focus of this chapter is antiglycaemic therapies, but the comprehensive treatment approach of T2DM is multi-factorial, as shown in the STENO-2 trial.[8] Drugs to control blood pressure and lipid levels are well-established treatments. Pushing these therapies too far, however, has shown their limits, particularly in T2DM with high risk for cardiovascular disease (CVD).[9,10] Even new aspirin guidelines call for tighter criteria for use in T2DM primary prevention.[11]

Medical nutrition and exercise therapy (MNET)

Medical nutrition and exercise therapy is unquestionably the foundation for T2DM prevention, antiglycaemia and CVD risk reduction. MNET should be prescribed to achieve treatment goals, preferably provided by a registered dietician familiar with diabetes education. The unresolved issue, however, is which target to use as a goal for MNET. Even though a body mass index (BMI) goal of <25 is recommended, this is not supported by the data. Based on BMI, over-weight and obese T2DM patients have the lowest rates of CVD and mortality compared with lower and higher BMI categories.[12] The 'U-shaped' relationship of BMI and CVD has been termed the 'obesity paradox' and probably reflects the fact that BMI does not accurately measure metabolically dangerous fat found in ectopic and intra-abdominal sites. Supine abdominal height, on the other hand, is a simple anthropometric measure and better predicts CVD risk and insulin sensitivity than BMI, waist girth and waist:hip ratio.[13]

Currently approved antiglycaemic therapies

Most physicians are feeling overwhelmed at the increasing number of antiglycaemics. If one of these drugs did the job, however, we wouldn't need so many (see Table 102.1). What the problems and needs are for approved and emerging antiglycaemics will be discussed.

Concerns about the benefits and harms of oral antiglycaemic medication have been with us since the UGDP (University Group Diabetes Program) study in 1970, which reported increased mortality and CVD risk with an SU (tolbutamide). Although in 1998 the UKPDS (United Kingdom Prospective Diabetes Study) was thought to have resolved this controversy, one arm in the study showed increased mortality and CVD risk when metformin was added to an SU (UKPDS34). In 2007, concern was again raised, this time for another drug, rosiglitazone, which was associated with excess mortality and CVD.[14]

Evaluating the safety and benefits of antiglycaemics is difficult because of the wide variability between classes and the number of drugs in each class. Furthermore, the hard outcomes data beyond glucose lowering are usually not available when making therapeutic decisions.

Even he US Congress is concerned. It directed the Agency for Healthcare Research and Quality (AHRQ), to evaluate the outcomes, comparative clinical effectiveness and appropriateness of prescription drugs, including antiglycaemics. Its report concluded that the evidence from clinical trials about drug efficacy on major clinical endpoints, such as cardiovascular mortality, is inconclusive.[15] Therefore, the whole area of T2DM therapeutics is filled with uncertainty. The US Food and Drug Administration (FDA) is making a small step in the right direction since it is requiring all new T2DM drug approvals to examine CVD endpoints and at least show no harm.

Metformin: life begins at 50

Metformin is on just about everyone's list of first-line antiglycaemics. Metformin been around for many years, beginning as *Galega officinalis* (French lilac) used in mediaeval Europe to treat many medical problems, including diabetes.[16] Fifty years ago, metformin was isolated from this plant and introduced for the treatment of T2DM. Since then, it has become the most widely prescribed diabetic therapy and with good reason. Metformin lowers glucose with

Table 102.1 Approved T2DM antiglycaemic therapies.

Class	Generic name	Trade name	Generic	Approved
Orals				
Sulfonylurea (SU)	Glipizide	Glucotrol	Yes	May 1984
		Glyburide DiaBeta, Glynase, Micronase		
	Glimepiride	Amaryl	Yes	November 1995
Biguanide	Metformin	Glucophage	Yes	March 1995
α-Glucosidase inhibitor	Acarbose	Precose	No	September 1995
	Miglitol	Glyset	No	December 1996
Thiazolidinedione (TZD)	Rosiglitazone	Avandia	No	June 1999
	Pioglitazone	Actos	No	July 1999
Meglitinide (glinide)	Repaglinide	Prandin	No	December 1997
	Nateglinide	Starlix	No	December 2000
DPP-4 inhibitor	Sitagliptin	Januvia	No	October 2006
	Saxagliptin	Onglyza	No	July 2009
Bile acid sequestrant	Colesevelam	Welchol	No	January 2008
Dopamine agonist	Bromocriptine	Cycloset	No	May 2010
SU and biguanide	Glyburide and metformin	Glucovance	Yes	July 2000
Biguanide and glitazone	Rosiglitazone and metformin	Avandamet	No	October 2002
Sulfonylurea and glitazone	Rosiglitazone and glimeriride	Avandaryl	No	November 2005
Biguanide and DPP-4 Inhib	Sitagliptin and metformin	Janumet	No	March 2007
Injectables				
Regular insulin	Human insulin (regular)	Humulin R, Novolin R	Yes	October 1982
Intermediate-acting insulin	Human insulin (NPH insulin)	Humulin N, Novolin N	Yes	October 1982
Human insulin combinations	Insulin regular and NPH insulin	Humulin 70/30	Yes	April 1989
Rapid-acting insulin analogues	Insulin lispro	Humalog	No	June 1996
	Insulin aspart	Novolog	No	June 2000
	Insulin glulisine	Apidra	No	April 2004
Long-acting basal insulin analogues	Insulin glargine	Lantus	No	April 2000
	Insulin detemir	Levemir	No	June 2005
Combinations (including analogues)	Insulin lispro/protamine	Humalog Mix 75/25 and 50/50	No	December 1999
	Insulin aspart-protamine	Novolog Mix 70/30	No	November 2001
Amylin analogue	Pramlintide	Symlin	No	March 2005
GLP-1 receptor agonist	Exenatide	Byetta	No	April 2005
	Liraglutide	Victoza	No	January 2010

negligible hypoglycaemia and measurable body weight loss. It decreases microvascular complications and one substudy of the UKPDS(34) showed a reduction in CVD and mortality as monotherapy in obese T2DM.

Metformin works by preventing hepatic gluconeogenesis through activation of AMP-activated protein kinase (AMPK), which in turn inhibits the expression of other hepatic gluconeogenic genes (e.g. PEPCK, phosphoenolpyruvate carboxykinase). Inhibition of gluconeogenesis lowers glucose production, but also reduces hepatic lactate uptake. Conditions which increase lactate production [alcohol intoxication, low-flow states, congestive heart failure (CHF), respiratory failure] combined with impaired renal clearance will potentially result in lactic acidosis. The most common adverse effects are diarrhoea and decreases in vitamin B_{12} levels.

Metformin has shown an anti-cancer effect compared with SU and insulin in observational studies.[7] The

mechanism may be through activation of AMPK, which plays a role in tumour suppression. Beyond the cancer preventive effect, there is evidence that metformin may enhance chemotherapy for existing cancers.[17]

The bottom line is that this drug deserves to be first-line. It is cheap, effective and has outcomes data. Unfortunately, metformin does not halt T2DM progression and most patients will move on to need another drug; the big question is, which one?

Sulfonylureas (SUs)

'*Special warning on increased risk of cardiovascular mortality*' is how the SU class label reads resulting from the 1970 UGDP study. There is some biological plausibility because SUs block 'ischaemic preconditioning', which is a mechanism for protecting the myocardium during periods of ischaemia. SUs bind to the potassium (KATP) channel, leading to an increase in intracellular potassium ion concentrations, thereby opening voltage-gated calcium channels, resulting in an influx of calcium ions. In pancreatic β-cells, this calcium influx promotes insulin secretion, but in the heart it impairs 'ischaemic preconditioning'.

Most of the physicians who know about the package label warning are reassured by results of the UKPDS33 trial (but not the UKPDS34 trial) and the positive recommendations by the ADA, AACE and other experts. Also, SUs are inexpensive and effective at lowering both glucose and microvascular complications. The good news is that SUs are probably safe, but the bad news is that they do not work to lower CVD and mortality. SUs also do not halt the progression of T2DM, so should we still be using them?

Meglitinides (glinides): faster is not always better

This class of drugs can be thought of as a rapid-acting SUs. Although they are non-SUs chemically, they act through the same mechanism to stimulate insulin secretion. Because of the rapid onset and short duration of action, glinides are best used to lower postprandial glycaemia (PPG). This means that they have to be dosed before each meal several times per day, which makes them inconvenient. Other negative points include hypoglycaemia, measurable weight gain and lack of positive outcomes data.

The best hope for success for glinides was to show that targeting PPG would improve CVD and prevent progression of T2DM. Previous studies have suggested that PPG was an even greater risk for CVD than fasting plasma glycaemia (FPG) for people with glucose intolerance (DECODE study). Unfortunately, this hope was dashed when pre-meal glinide (nateglinide) therapy failed to show any CVD protection or slowing of the progression of hyperglycaemia.[18] Therefore, this appears to be another drug class that is lacking in efficacy.

Thiazolidinediones (TZDs): the bloom is off the rose and the pie is in the sky (rosiglitazone and pioglitazone) – downsizing expectations

At first, this class of drugs promised benefits beyond glucose reduction, as suggested by encouraging surrogate outcomes for CVD. Insulin resistance, interleukin-6 and VEGF-induced angiogenesis all decreased, adiponectin levels rose and visceral fat moved to the periphery. Among the positive attributes, TZDs do not produce hypoglycaemia and they slow the progression of β-cell loss. Compared with SUs and metformin, rosiglitazone has greater durability as monotherapy (ADOPT – A Diabetes Outcome Progression Trial).

The bloom fell off the rose, however, when a controversial meta-analysis for rosiglitazone changed the discussion from potential CVD efficacy to concerns over CVD safety. Subsequent CVD outcomes studies have not shown increased mortality, but neither have they shown much benefit (PROACTIVE and RECORD trials). The main safety concerns with this class is a fourfold increase in CHF and an acceleration of bone loss resulting in a doubling of fracture rates. TZDs' best benefits, however, may be prevention of T2DM, which is achieved at lower doses, thereby reducing these safety concerns.[19]

α-Glucosidase inhibitors (AGIs) – the drugs that get no respect

Drugs in this class are frequently the butt of jokes and no one takes them seriously. Like Rodney Dangerfield, these drugs 'don't get no respect', which is unfortunate given all of their positive attributes. Their mechanism of action is simple: they block the digestion and absorption of ingested polysaccharides, thus reducing the level of postprandial glucose and insulin excursions. Although the major impact is on postprandial glucose, they also reduce fasting glucose and HbA1c. This class of drugs has many positive features: no hypoglycaemia, consistent loss of body weight and the progression of T2DM is slowed. Blood pressure, triglycerides, inflammatory biomarkers and the development of hypertension are all reduced. Even better, these positive surrogate markers result in positive outcomes as measured by reduced progression of atherosclerosis (vascular intimal medial thickness) and cardiovascular events in an impaired glucose-tolerant (IGT) population (STOP-NIDDM trial). Even though this is a very safe drug class, almost half of the patients will have gastrointestinal complaints. Carbohydrate is usually absorbed in the upper intestine; upon initiation of AGIs, a large portion escapes

digestion and is delivered to the colon causing excessive bacterial activity. To avoid this, AGIs should be titrated slowly over several months, giving time for the lower small intestine to acquire the ability to absorb carbohydrates.

AGIs are a good fit with metformin, although both have gastrointestinal side effects. AGIs are particularly effective in mild hyperglycaemia and in correcting postprandial hyperglycaemia. AGIs have CVD outcomes data and are very safe. These drugs should be thought of more often when prescribing antiglycaemics.

Colesevelam: LDL and A1c lowering – a match made in heaven

The bile-acid binding resin colesevelam was approved for LDL lowering in 2000 and 8 years later for glucose lowering in T2DM. This class of drugs has already been shown to reduce CVD and mortality, although not in a T2DM population.

The mechanism for colesevelam's antiglycaemic action is unknown, but the alteration in bile acid composition produces two possible antiglycaemic actions: (1) increased delivery of fatty acids to the distal intestine stimulating GLP-1 secretion and (2) activation of hepatic FXR (farnesoid X receptor), which inhibits gluconeogenesis. The combination of increased GLP-1 action and decreased hepatic gluconeogenesis is like combining a DPP4I (dipeptidylpeptidase-4 inhibitor) with metformin (e.g., Janumet).

To date, colesevelam does not have micro- or macrovascular endpoint data, but it does lower both glucose and LDL with negligible hypoglycaemia and weight changes.[20] Colesevelam's LDL-lowering effects are additive with statins. The combination of colesevelam and a statin permits a reduction in the statin dose and risk of rhabdomyolysis and attenuates the rise in triglycerides observed with this class of drugs.

Because it is a bile acid-binding resin, it does not have systemic effects, but the main complaints are gastrointestinal. Recently, a convenient single-dose packet dissolved in a glass of water has replaced the onerous six capsules daily.

Bromocriptine: born again

Physicians have been using this drug for many years to treat prolactin-secreting pituitary tumours, Parkinson's disease and many other off-label uses. Now it has been re-born as a quick-release formulation, Cycloset (0.8 mg tablets, VeroScience), to treat T2CM as an adjunct to diet and exercise.[21]

This is the only antiglycaemic believed to work through the central nervous system. Obese, insulin-resistant T2DM patients have twofold elevated plasma prolactin levels, indicating a hypothalamic dopamine deficiency. Administered as a single timed morning dose, this centrally acting dopamine D2 receptor agonist acts on circadian neuronal activities within the hypothalamus to reset abnormally elevated prolactin, plasma glucose, triglyceride and free fatty acid levels in fasting and postprandial states in insulin-resistant patients.

Bromocriptine may be used as monotherapy or combined with other oral antiglycaemics; use with insulin has not been studied. The recommended starting dose of bromocriptine is 0.8 mg daily and is increased in 0.8 mg increments weekly until the target range (1.6–4.8 mg) or until maximum tolerance is reached. Doses should be administered once daily within 2 h of waking in the morning and with food to reduce the risk for gastrointestinal tract adverse effects such as nausea.

Adverse events most commonly reported in clinical trials of bromocriptine included nausea, fatigue, vomiting, headache and dizziness. These events lasted a median of 14 days and were more likely to occur during initial titration of the drug. None of the reports of nausea or vomiting were described as serious.

Bromocriptine was the first diabetes drug to be approved under the FDA's new guidelines requiring clinical trials to demonstrate no increased cardiovascular risk. In a 52 week double-blind, placebo-controlled safety trial ($n = 3000$), treatment with bromocriptine did not increase the risk for a composite of myocardial infarction, stroke, hospitalization for unstable angina, CHF and revascularization surgery. In fact, the risk of this composite CVD endpoint was reduced (hazard ratio, 0.58; 95% confidence interval, 0.35–0.96). This drug appears also to be a good fit as a second agent with metformin and the positive (but preliminary) CVD data are encouraging.

Incretin therapies: the new kid on the block

Incretin therapy is the new class of antiglycaemic therapies which has generated the most excitement. Incretins are a group of gastrointestinal hormones including glucagon-like peptide-1 (GLP-1) which are secreted into the circulation when nutrients reach the small intestinal. Incretins (like GLP-1) travel to the pancreas, where they stimulate insulin and suppress glucagon secretion in a glucose-dependent manner. They also delay gastric emptying and promote satiety. GLP-1 is rapidly inactivated by the enzyme dipeptidylpeptidase-4 (DPP-4). Of the known incretins, GLP-1 has the greatest antiglycaemic activity and therapeutic GLP-1 analogues have been developed. The other incretin strategy is to inhibit DPP-4 and prolong the action of endogenous incretins. We will compare and contrast these drugs between and within classes.

Table 102.2 GLP-1 agonist and DPP4 inhibitor comparisons.

Item	GLP-1 agonists	DPP-4 inhibitors
Route of administration	Subcutaneous	Oral
Gastrointestinal side effects (fullness, nausea and vomiting)	Yes	No
Weight changes	Weight loss	Weight neutral
Selectivity	GLP-1 receptor only	Multiple substrates – GLP-2, NPY, SP, PACAP, others
Increase in GLP-1 activity	Supraphysiological	Near physiological and retained diurnal pattern
Gastric emptying	Delayed	Normal
Drug overdose	Problematic	Non-toxic
Plasma glucose	↓FPG (liraglutide only) and marked ↓PPG	↓FPG and slight ↓PPG
A1c reduction	1.0–2.0%	0.5–1.0%
Glucagon suppression	More	Less
Increased β-cell mass	Yes	Not known
Increased glucagon counter-regulation with hypoglycaemia	Yes	Not known
Severe renal failure	Not recommended	Dose adjustment

Comparing GLP1 agonist and DPP4 inhibitors

Both GLP-1 agonist and DPP4 inhibitors are antiglycaemic, with GLP-1s being more potent.[22] Both classes share the following attributes: (1) negligible hypoglycaemia because the insulin secretion is 'glucose dependent'; (2) neutral (DPP4I) or negative (GLP1) body weight changes; (3) suppression of pancreatic α-cell glucagon secretion; and based on animal data, incretin therapies may (4) potentially slow the progression of β-cell loss and (5) potentially reduce CVD through improved risk factor profile and direct CV protection.[23] (see Table 102.2).

GLP-1 agonists

Two GLP-1 agonists have been approved for use: exenatide and liraglutide; a comparison of their clinical characteristics is given in Table 102.3. Pharmacokinetics and immunological reactions are the main differences. Liraglutide has greater antiglycaemia effect and probably less gastrointestinal symptoms, probably because of a flatter and prolonged blood level. Future GLP-1 agonists will have even longer half-lives, allowing for once weekly dosing. The main concerns regarding GLP-1 agonists include medullary thyroid cancer and pancreatitis.

Table 102.3 GLP-1 agonist comparisons: exenatide (Byetta) and liraglutide (Victoza).

Item Dose schedule	Exenatide Twice daily	Liraglutide Once daily
Blood levels	Peak and trough blood levels	Flat blood levels
Weight changes	Weight loss	Weight loss
Antiglycaemia	Lowers A1c and PPG	Lowers A1c, PPG and FPG
Antibodies	Antibodies	No antibodies
Skin reaction	Positive injection site reactions	No injection site reactions

Medullary thyroid cancer

Rodent data show that GLP-1 agonist therapy increases calcitonin levels and produces c-cell hyperplasia and cancer. This is probably not a concern in humans, however, since calcitonin levels do not increase, there is no c-cell hyperplasia and there are no reports of medullary thyroid cancer in over one million patients exposed to exenatide.

Pancreatitis

Pancreatitis is more of a concern with incretin therapies (both GLP-1a and DPP4I), but still a rare occurrence. The connection was first suspected because of the overlap of the venoms from the scorpion, known to produce pancreatitis, and Gila monster, from which exendin 4 (exenatide) was isolated. It should be noted that T2DM itself has a threefold greater risk of pancreatitis (4.2 versus 1.5 per 1000 patient-years).

The precise risk and causality of pancreatitis with incretin therapy are unknown. Pancreatitis case reports for both exenatide and sitagliptin, however, have prompted new

package labelling. Definitive data on the pancreatitis risk are lacking and the studies are mixed. Clinical trials of liraglutide showed about three times more pancreatitis than the comparator (2.2 versus 0.6 cases per 1000 patient-years). However, the numbers are very small, seven versus one. In addition, one study using an insurance claims database found no increase in pancreatitis with either exenatide (0.13%) or sitagliptin (0.12%) compared with metformin or glyburide users for up to 1 year. In conclusion, pancreatitis is a rare occurrence in incretin therapy users and the association is unclear. Nevertheless, caution dictates that one should avoid using incretin therapy in patients with chronic pancreatitis or at risk for this disease.

DPP4 inhibitors

One can think of DPP4 inhibitors as GLP-1's younger sibling – not quite as strong or as fast but safer and less likely to cause trouble. Compared with the GLP-1 agonists, DPP4Is have less antiglycaemia, glucagon suppression and weight loss effects, but they also are non-toxic, can be used in severe renal failure and have almost no adverse effects.[22] One potential advantage DPP4Is have as a class is that they increase levels of a wider range of incretins than just GLP-1. These additional incretins could have benefits above and beyond GLP-1, for example, β-cell neogenesis. Sitagliptin, the first DPP4I, was approved before FDA's CVD guidelines were in place. Saxagliptin, approved later, satisfied the FDA guidelines by demonstrating a 50% reduction in CVD endpoints.[23]

DPP4 inhibitors, ACE inhibitors and angioedema

One potential downside of DPP4Is is complications arising from inhibiting other non-incretin actions of this enzyme. For example, combining DPP4I with an acetylcholinesterase (ACE) inhibitor decreases the degradation and increases the levels of some of the vasoactive peptides linked to angioedema.[24] Angiotensin receptor blockers (ARBs) do not share the same risk and may be an alternative to ACE inhibition when there is concern about angioedema.

Amylin analogues – pramlintide

Amylin is co-secreted with insulin from pancreatic β-cells and acts centrally to slow gastric emptying, suppresses postprandial glucagon secretion and decreases food intake. Amylin is relatively deficient in patients with T2DM and essentially absent in T1DM. Pramlintide is an amylin analogue that has been shown to improve glycaemic control via reductions in postprandial glucose and to reduce bodyweight. Pramlitide is usually given as a meal-time subcutaneous injection bolus with the advantage of less hypoglycaemia and weight gain compared with bolus insulin.

Emerging but not yet approved antiglycaemics

If we had the perfect treatment for T2DM we would not need new therapies, and if lowering glucose were the only criteria then we could stop now. So what are the characteristics and unmet needs of the current antiglycaemics that new drugs should target? (see Tables 102.4 and 102.5).

Prevention and progression – too fat, too lazy and too little insulin

The pathophysiology of T2DM involves two hits: the first is that it starts with insulin resistance partly as a result of

Table 102.4 Approved antiglycaemics and their selected characteristics[a].

Drug	Insulin levels	Insulin sensitivity	β-Cell	PPG	Hypo	BW	RF	CVD
Metformin	↔	↑	↔	↔	↔	↓	↓	↓*
TZD	↔	↑	↑	↔	↔	↑	↓	↔
AGI	↔	↔	↔	↓	↔	↓	↓	↓**
SU	↑	↔	↔	↓	↑	↑	↔	↔
Glinide	↑	↔	↔	↓	↑	↑	↔	NR
Insulin	↑	↔	↔	↓	↑	↑	↔	↔
Amylin	↔	↔	↔	↓	↔	↓	↔	NR
GLP-1a	↑	↔	↑	↓	↔	↓	↓	NR
DPP4I	↑	↔	↑	↓	↔	↔	NR	↓***
Colesevelam	↔	↔	NR	0	↔	↔	↓	↓****
Bromocriptine	↔	↓	NR	↓	↔	↔	NR	↓*****

[a]β-Cell = β-cell function or mass; Glucose = blood glucose levels; Hypo = hypoglycaemia; BW = body weight; RF = CVD risk factors; ↓* = UKPDS34 in obese T2DM as monotherapy, STOP-NIDDM in IGT reduced CVD and hypertension; ↓*** = saxagliptin in the FDA registration trials; ↓**** = class effect; ↓***** = in the FDA registration trials; NR = not reported.

Table 102.5 Antiglycaemic therapy's unmet needs.

1	*Prevention of T2DM* – improve insulin sensitivity
2	*Progression of insulin deficiency* – stop progressive β-cell loss
3	*Reduce postprandial glycaemia* – slow carbohydrate absorption or augment insulin secretion
4	*Prevent hypoglycaemia* – insulin secretion should be glucose dependent
5	*Prevent increasing body weight* – avoid increasing visceral or ectopic adiposity
6	*Improve CVD risk factors* – reduce blood pressure and LDL
7	*Reducing CVD and mortality* – the important but elusive goal

our lifestyle and the second is insulin deficiency from β-cell failure. Diet and exercise, although helpful, have not been the answer and we do not have a proven drug (although several candidates) which can restore β-cell function.

Postprandial glycaemia (PPG) – the stealth defect

In the early stages of T2DM, meal-related bolus insulin release is the first defect and in later stages it is the hardest defect to correct. In addition, PPG is a stealth defect and goes unnoticed because it is so difficult to detect.

Hypoglycaemia – the limiting factor

The closer T2DM glucose levels get to normoglycaemia, the greater is the risk of hypoglycaemia. There is hope, however. Newer insulin secretogogue therapies have the property of 'glucose dependency', meaning that insulin will not be secreted unless there are adequate levels of circulating glucose.

Weight gain

Insulin and SUs are noted for weight gain. The negative CVD consequences of weight gain, especially visceral and ectopic fat, may offset the positive effect of glucose lowering. It is encouraging that many of the newer antiglycaemics are either weight neutral or promote weight loss. The mechanisms are probably different for each class of medication but are generally thought to be related to reduced gastric emptying, enhanced metabolism or central appetite suppression.

Cardioprotection

Therapies are needed that will reverse the cardiovascular disease and mortality burden imposed by hyperglycaemia. This goal is arguably the most important, but also the most difficult, since very large and very long studies are required.

Developing antiglycaemic classes and their characteristics

A selection of developing antiglycaemic classes and their selected characteristics are described below (see Tables 102.6 and 102.7).

Dual and pan PPAR agonists: a fibrate, TZD, and exercise all in one pill

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes involved in glucose, lipid and energy homeostasis.[25] The PPARs come in three types: α, γ and δ; α regulates triglyceride synthesis and energy homeostasis, γ regulates insulin sensitivity and glucose metabolism and δ enhances fatty acid metabolism.

Since T2DM is characterized by multiple metabolic defects, including dysglycaemia and dyslipidaemia, the PPARs are an attractive therapeutic target. Single PPAR agonists in the fibric acid drug class (PPAR-α agonists: clofibrate, gemfibrozil, ciprofibrate, bezafibrate and fenofibrate) and TZDs (PPAR-γ: rosiglitazone and pioglitazone) are already in use. Interest in dual and pan PPAR agonists (α–γ, α–δ, γ–δ and α–γ–δ) may lead to drugs that combine the actions of a TZD on hyperglycaemia and a fibrate drug on hypertriglyceridaemia and more.

However, the road for dual PPARs has been filled with potholes. Two of the most senior drugs in this class have been discontinued: tesiglitazar (Galidea) for decreasing glomerular filtration rate and muiraglitazar (Pargluva) for increasing cardiovascular events. Hope springs eternal, however, and another dual PPAR, aleglitazar, has shown a glucose-lowering effect, favourable lipid modifications and a good safety profile.

PPAR-δ agonists are perhaps the most interesting, and one of them has been termed the 'exercise pill'. Used alone, PPAR-δ can shift glucose utilization to fatty acid oxidation, which could reverse the metabolic abnormalities in obesity. When combined with an adenosine-augmenting agent, AICAR (aminoimidazole carboxamide ribonucleotide), the PPAR-δ agonist (GW1516) changes skeletal muscle phenotype to become more insulin sensitive, thus improving glucose homeostasis and mimicking the effects of exercise.[26]

SGLT2 inhibitors: now diabetics can eat that piece of cake without feeling guilty

Sodium glucose transport (SGLT) T2 inhibitors may lead to a paradigm shift of how we think about T2DM patients and their diets. With these drugs, T2DM patients can have their cake and eat it too, because the extra sugar can be excreted in the urine. The mode of action involves inhibiting SGLT2, which is responsible for 90% of renal glucose reabsorption. Inhibiting reabsorption results in glycosuria and blood

Table 102.6 Antiglycaemics in development.

Mechanism	Drug	Company	Target	Development (phase)
11BHSD inhibitor	11BHSD	Bristol-Myers Squibb	DM	Clinical trials
11BHSD inhibitor	AMG 221	Amgen	T2DM	P 1
11BHSD inhibitor	INCB-13739, 19602, 20817	Incyte	T2DM	P 2
11BHSD inhibitor	JTT 654	Japan Tobacco	T2DM	P 1
ACE inhibitor	Altace (ramipril)	King Pharmaceuticals	T2DM prevention	P 3
Adenosine receptor agonist	ATL-844 (Stedivaze, adenosine receptor agonist)	PGxHealth	T2DM	P 2
Anti-inflammatory	AMG 108 (IL-1 receptor antagonist)	Amgen	DM	P 2
	AVR 118 (chemokine/cytokine modulator)	Advanced Viral Research	T2DM	P 1
	BMS-741672 (CCR2 antagonist)	Bristol-Myers Squibb	DM	Clinical trials
	VGX-1027 (cytokine inhibitor)	VGX Pharmaceuticals	T1DM	P 1
	XOMA052 (interleukin inhibitor)	XOMA	T2DM	P 1
Anti-obesity	CE-326597 (CCK receptor antagonist)	Pfizer	T2DM	P 2
	Cetilistat (gut lipase inhibitor)	Alizyme	T2DM	P 2
Antioxidant	Succinobucol	AtheroGenics	T2DM	P 3
Antoimmune	Teplizumab	Eli Lilly	T1DM	P 2/3
	Autoimmune DM vaccine	Diamyd Medical	T1DM	P 3
	Canakinumab	Novartis Pharmaceuticals	T2DM	P 2/3
	DiaPep277	Andromeda Biotech	Latent autoimmune DM	P 2
	Larazotide	Alba Therapeutics	T1DM	P 1
	Lisofylline	DiaKine Therapeutics	T1DM	P 1
	NBI-6024	Neurocrine Biosciences	T1DM	P 2
	Otelixizumab	Tolerx	T1DM	P 2
	PEG-encapsulated islet cell	Novocell	T1DM	P 1/2
	Prochymal (stem cell Rx)	Osiris Therapeutics	T1DM	P 2 + A7
β-Cell regeneration	INGAP peptide	Kinexum Metabolics	T1DM	P 2
Biguanide	MetControl (metformin buccal)	Generex Biotechnology	T2DM	P 2
CFTR inhibitor	NP-500 (cystic fibrosis transmembrane conductance regulator inhibitor)	Napo Pharmaceuticals	T2DM	P 1
Cortisol Inhibitor	DIO-902 [(2S, 4R)-ketoconazole, cortisol inhibitor]	DiObex	T2DM	P 2
DPP4 inhibitor	ABT-279, alogliptin	Abbott Laboratories	T2DM	P 1
	Alogliptin	Takeda Pharmaceuticals	T2DM	Clinical trials
	Alogliptin/pioglitazone	Takeda Pharmaceuticals	T2DM	Clinical trials
	AMG 222	Amgen	T2DM	P 2
	ARI-2243 (Arisaph)	Arisaph Pharmaceuticals	T2DM	P 1

(*continued overleaf*)

Table 102.6 (*continued*).

Mechanism	Drug	Company	Target	Development (phase)
	BI-1356 (Ondero)	Boehringer Ingelheim	T2DM	P 3
	Galvus (vildagliptin)	Novartis Pharmaceuticals	T2DM	Application
	KRP 104	ActivX Biosciences	T2DM	P 2
	MP-513	Mitsubishi Pharma	T2DM	P 1
	PF-734200	Pfizer	T2DM	P 2
	PHX-1149 (dutogliptin)	Forest Laboratories	T2DM	P 3
	R1579	Roche	T2DM	P 2
	Saxagliptin/metformin	AstraZeneca/BMS	T2DM	P 3
	SYR-472	Takeda Pharmaceuticals	T2DM	P 2
	TA-6666	Mitsubishi Pharma	T2DM	P 2
	Vildagliptin/metformin	Novartis Pharmaceuticals	T2DM	Clinical trials, resubmission?
FBPase inhibitor	MB07803	Metabasis Therapeutics	T2DM	P 2
Fibroblast growth factor	LP-10152 (FGF-21)	Eli Lilly	T2DM	P 1/2
Gastrin analogue	TT-223 and epidermal growth factor analogue	Eli Lilly	T1DM	P 2
	TT-223 and GLP-1 analogue	Eli Lilly	T1DM	P 1
	TT-223 and metformin	Eli Lilly	T1DM	P 2
Glucokinase agonist	AZD6370, 1656	AstraZeneca	T2DM	P 1
	Glucokinase activator	Bristol-Myers Squibb	DM	Clinical trials
	LY-2599506	Eli Lilly	T2DM	P 1
	LY-2121260	Eli Lilly	T2DM	P 1
	MK-0599	Merck	DM	P 1
	R1511	Roche	T2DM	P 1
	R4929	Roche	T2DM	P 1
	TTP355	TransTech Pharma	T2DM	P 1
Glinide	Metgluna (mitiglinide/metformin)	Elixir Pharmaceuticals	T2DM	P 3
GLP-1 agonist	756050 (albiglutide)	GlaxoSmithKline	T2DM	P 1
	AVE0010 (GLP-1a)	Sanofi-aventis	T2DM	P 2
	AVE0010 (GLP-1a XR)	Sanofi-aventis	T2DM	P 1
	Exenatide intranasal	Amylin Pharmaceuticals	T2DM	P 1
	LY-2189265	Eli Lilly	T2DM	P 2/3
	LY-2405319	Eli Lilly	T2DM	P 2
	R1583	Roche	T2DM	P 2
	SUN E7001	Asubio Pharma	T2DM	P 1
	Taspoglutide	Roche	T2DM	P 2
Glucagon receptor antagonist	AMG 477	Amgen	T2DM	P 1
	ISIS 32568	Isis Pharmaceuticals	T2DM	P 1
GPR-119 agonist	APD688	Arena/Ortho-McNeil-Janssen	T2DM	P 1
Guanidine	Pyrazolylguanidine	SuperGen	T2DM	P 2
Insulin	AI-401 (oral/nasal insulin)	AutoImmune	T1DM prevention	P 3
	Alveair (inhaled insulin)	Coremed	DM	P 1

Table 102.6 (*continued*).

Mechanism	Drug	Company	Target	Development (phase)
	AT1391 (insulin skin patch)	Altea Therapeutics	T1DM	P 1/2
	BHT-3021	Bayhill Therapeutics	T1DM	P 1/2
	Bydureon (exenatide XR)	Amylin Pharmaceuticals	T2DM	Submitted application
	HDV insulin (hepatic directed vesicle)	Diasome Pharmaceuticals	T2DM	P 2
	Insulin inhalation	Baxter Healthcare	DM	P 1
	Insulin inhalation	MicroDose Technologies	DM	P 1
	Insulin nasal spray	MDRNA	T2DM	P 2
	Insulin oral	Generex Biotechnology	DM	P 3
	Insulin transdermal	Dermisonics	T1DM	P 1
	Intesulin (oral insulin)	Coremed	DM	P 1
	Nasulin (intranasal insulin)	CPEX Pharmaceuticals	DM	P 2
	NN1250 (Degludec insulin)	Novo Nordisk	DM	Clinical trials
	Oral insulin using Eligen technology	Emisphere Technologies	T2DM	P 1/2
	rHuPH20 (hyaluronidase/insulin)	Halozyme Therapeutics	DM	P 1
	Technosphere (inhaled insulin)	MannKind	DM	Clinical trials
	VIAject (rapid insulin)	Biodel	T1DM	P 3
	VIAtab (oral/sublingual insulin)	Biodel	T1DM	P 1
	Albulin (albumin/insulin)	Teva Pharmaceuticals USA	T1DM	P 1
Insulin secretogogue	Glinsuna (mitiglinide)	Elixir Pharmaceuticals	T2DM	P 3
(glucose-dependent)	MBX-2982 (GPR-119)	Metabolex	T2DM	P 1
Insulin sensitizer	CRx-401 (benzafibrate + diflunisal)	CombinatoRx	T2DM	P 2
	CVT-3619 (adenosine receptor agonist)	CV Therapeutics	DM	P 1
PPAR agonist	376501	GlaxoSmithKline	T2DM	P 1
	625019	GlaxoSmithKline	T2DM	P 1
	Avandamet XR (extended release)	GlaxoSmithKline	T2DM	P 3
	Avandia (rosiglitazone)	GlaxoSmithKline	T2DM prevention	P 3
	AVE0897 (balanced PPAR agonist)	Sanofi-aventis	T2DM	P 1
	Balaglitazone	Dr. Reddy's Laboratories	T2DM	P 3
	INT-131	InteKrin Therapeutics	T2DM	P 2
	K 111	Kowa Pharmaceuticals	T2DM	P 2
	MBX-102 (non-TZD, metaglidasen)	Johnson & Johnson	T2DM	P 2/3
	MBX-2044	Johnson & Johnson	T2DM	P 2
	MCC-555 (netoglitazone)	Mitsubishi Pharma	T2DM	P 2
	MSDC-0160	Metabolic Solutions	T2DM	P 2

(*continued overleaf*)

Table 102.6 (*continued*).

Mechanism	Drug	Company	Target	Development (phase)
	Netoglitazone	Perlegen Sciences	T2DM	P 1
	ONO-5129	Ono Pharma USA	T2DM	P 2
	PPM-204 (indeglitazar)	Plexxikon	T2DM	P 2
	R1439 (aleglitazar)	Roche	T2DM	P 2
	Rivoglitazone	Daiichi Sankyo	T2DM	P 3
	Sodelglitazar	GlaxoSmithKline	T2DM	P 2
PYY3-36 analogue	PF-4325667	Pfizer	DM	P 1
SGLT2 inhibitor	AVE2268 (SGLT2 inhibitor)	Sanofi-aventis	T2DM	P 2
	BI-10773	Boehringer Ingelheim	T2DM	P 1
	BI-44847	Boehringer Ingelheim	T2DM	P 2
	Dapagliflozin (SGLT2 inhibitor)	AstraZeneca/BMS	DM	P 3
	Dapagliflozin/metformin	AstraZeneca/BMS	T2DM	P 3
	R7201	Roche	T2DM	P 1
	Remogliflozin	GlaxoSmithKline	T2DM	P 2
	SAR7226 (SGLT1/2 inhibitor)	Sanofi-aventis	T2DM	P 1
	TA-7284 (canagliflozin)	Johnson & Johnson	T2DM	P 1
	YM543	Astellas Pharma US	T2DM	P 2
Sirtuin-1 activator	SRT-2104 (resveretrol analogue)	Sirtris Pharmaceuticals	T2DM	P 1
Sweetener	Naturlose (tagatose)	Spherix	T2DM	P 3
Synthetic steroid	HE-3286 (synthetic steroid)	Hollis-Eden Pharma	T2DM	P 2
TGR5 agonist	INT-777	InteKrin Therapeutics	T2DM	P 2
Tyrosine phosphatase inhibitor	ISIS 113715(tyrosine phosphatase inhibitor)	Isis Pharmaceuticals	T2DM (combo Rx)	P 2
	Trodusquemine (MSI-1436)	Genaera	T2DM	P 1
Vanadium	AKP-020 (vanadium compound)	Akesis Pharmaceuticals	T2DM	P 2

glucose lowering. Therefore, the meal excursions of glucose will be lost into the urine, making dietary restrictions of carbohydrate less important. Beyond antiglycaemia, SGLT2 inhibitors also reduce insulin levels and hepatic steatosis and improve β-cell function. In clinical trials, these drugs have shown a low risk of hypoglycaemia, measurable weight loss and reduced blood pressure.[27] On the other hand, an increase in genito-urinary infections has been noted. Future studies should help to resolve potential safety issues, including fluid and electrolyte imbalances and long-term renal function.

Insulin analogues and new delivery approaches: God did not make human insulin to be injected subcutaneously

The direction of insulin development is to be longer, faster and easier. We will not discuss advances in closed-loop patch pump therapies since those are primarily for T1DM. Insulin therapies have not been shown to reduce CVD or slow the progression of T2DM. Perhaps that is because insulin therapy is started very late in the course of the disease. To test whether earlier initiation of insulin therapy will address these problems, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial will start newly diagnosed T2DM and IGT patients on glargine insulin. The results of CVD reduction and T2DM progression are pending.

Basal insulin

SIBA (soluble insulin basal analogue, degludec) is a modified detemir molecule with a very flat, smooth-action profile lasting more than 24 h. It has the potential for thrice weekly dosing. Unlike current basal insulins, degludec can be mixed with a rapid-acting insulin to give basal/bolus therapy in one injection.

Table 102.7 Emerging antiglycaemics and their selected characteristics[a].

Class	Insulin levels	Insulin sensitivity	β-Cell	Glucose	Hypo	BW	RF	Comments
Dual PPAR agonist	↔	↑	↑	0	↔	↑	↓	Some have cardiac or renal toxicity
SGLT2 inhibitors	↔	?	↑	↓	↔	↔	↓	Genitourinary infections
Insulin analogues	↑	↔	?	↓	↑	↑	↔	Earlier insulin Rx may be needed to see benefits
Glucokinase agonists	↑	↔	↑	↓	↑	?	?	Hypos and collateral organ adverse events are of concern
FBPase inhibitors	?	?	?	↓	↔	?	?	Metformin-like with less lactate production
GPR119 agonists	↑	↔	↑	↓	↔	↓	?	Action may be augmented with DPP4I
TGR5 agonists	↑	↔	↑	↓	↔	↓	?	↑energy expenditure in brown fat and muscle
FABR agonists	↑	↔	?	↓	↔	?	?	Concern about lipotoxicity in β-cells
DGAT inhibitors	↔	↑	?	?	?	↓	?	Hepatic steatosis ↓
11BHSD inhibitors	?	?	?	?	?	?	?	Clinical studies have shown little efficacy
Oxyntomodulin analogues	↑	↔	?	↓	↔	↓	?	Combined GLP-1 and glucagon actions
SRBP inhibitor	?	↑	?	↓	?	↓	?	Concern about ↓ hepatic LDL receptor
Bariatric surgery	↑	↔	↑	↓	↔	↓	↓	↓in CVD and mortality demonstrated

[a]β-Cell = β-cell function or mass; Glucose = blood glucose levels; Hypo = hypoglycaemia; BW = body weight; RF = CVD risk factors.

Bolus insulin

VIAject is a formulation of human insulin which has been disassociated into the monomers by the addition of EDTA and citric acid. Pharmacokinetic data demonstrate a faster onset of action than lispro insulin.

New delivery approaches

Buccal, oral and dermal insulins have been under development for some time without much reported success. Nasal and inhaled insulins have been reported to have better absorption rates, but a previously approved inhaled insulin (Exubera) was taken off the market by its manufacturer (Pfizer) owing to poor sales. Before Exubera left the market, however, the FDA required labelling to include a warning for smokers about the risk for lung cancer.

Glucokinase activators: targeting two organs–pancreas and liver – with one pill

Glucokinase activators (GKAs) are a new class of T2DM drugs which target both the pancreas and liver. Glucokinase (GK) is an enzyme that catalyses the phosphorylation of glucose an important step in regulating glucose metabolism. In the β-cell GK activity serves as a glucose sensor for insulin release and in the liver it regulates glycogen production. The activity of this enzyme is regulated endogenously by regulatory proteins. GK activation by these proteins causes the β-cells and hepatocytes to 'sense glucose', thus releasing insulin and taking up glucose to make glycogen, respectively.

Pharmacological GK activation has been an attractive target for T2DM because it addresses two fundamental defects in T2DM: decreased insulin secretion and increased hepatic glucose output. GKA may also decrease β-cell failure, another problem in T2DM.[28]

Several GKAs undergoing clinical testing show efficacy in controlling both FPG and PPG and with other antiglycaemics, including insulin sensitizers and incretin-based therapies. Several concerns need to be resolved, however, including profound hypoglycaemia (the insulin secretion is not glucose dependent), GK activation in other tissues may have untoward effects (e.g. pituitary) and augmented hepatic lipid synthesis (with steatohepatitis). It is also notable that the development of one of most advanced GKAs, Piragliatin, by Hoffman-La Roche was discontinued for undisclosed reasons. Nevertheless, this is a very promising and active area of drug development.

Fructose 1,6-bisphosphatase (FBPase) inhibitors – a metformin mimic

Inhibition of hepatic gluconeogenesis with metformin has proved to be a very successful treatment strategy for T2DM. FBPase is a key enzyme in gluconeogenesis and it has an inhibitory AMP-binding site which is a therapeutic target. AMP mimetics which produce FBPase inhibition should have many of the same efficacy attributes as metformin. One candidate, MB07803 monotherapy, in recent T2DM clinical trials resulted in rapid and pronounced fasting and postprandial glucose lowering. This drug has less effect on lactate metabolism and acid–base balance, which have been problems with earlier compounds.

Antiglycaemic therapies that evolved from G protein-coupled receptor (GPCR) 'orphans'

The discovery of many orphan GPCRs resulted from identifying genes with sequence similarity from large genomic data pools. They were orphans because the ligand for the receptor had not yet been discovered. Some of these orphan GPCRs were involved in glucose and lipid metabolism. Subsequent discovery of their ligands, a strategy called 'deorphanization', has had an impact on drug discovery for T2DM – including a few discussed below: the bile acid-binding receptor TGR5, the fatty acid-binding receptors GPR40 and GPR120 and the glucose-dependent insulinotrophic receptor GPR119.

GPR119 agonists: this orphan has been adopted

GPR119 is a deorphanized GPCR located on β-cells of the pancreas, GLP-1-producing L-cells of the intestine and incretin-producing K-cells of the stomach. Although GPR119's physiological ligand is still uncertain, pharmacological agonists have been found which will produce glucose-dependent insulin secretion both directly and via GLP-1 and other incretins. Animal studies demonstrate glucose lowering, delayed gastric emptying, reduction of body weight, decreased glucagon secretion and preservation of β-cell loss. These effects can be augmented by concomitant DPP4 inhibition.

TGR5 (bile acid receptor) agonists: lower the glucose and raise the heat

Bile acids were once thought of as simple detergents to help with digestion. New evidence, however, points to bile acids as potent hormones helping to regulate body metabolism and glucose homeostasis. Bile acids appear to function as nutrient signalling molecules when they return from the intestines to the liver following a meal. Bile acids bind to several receptors, including the GPCR TGR5, which increases the conversion of the thyroid hormone T4 to its active product T3 and in the gut stimulates GLP-1 secretion. The conversion of T4 to T3 is intracellular in brown fat and muscle and T3 does not enter the circulation, thereby avoiding a state of hyperthyroidism.

The dual antiglycaemic and hypermetabolic actions of TGR5 could complement each other in T2DM therapy. TGR5 agonists have been synthesized with this idea in mind.[29] In animal studies, INT-777, a TGR5 agonist, has been shown to stimulate GLP-1 levels, improve glucose tolerance, protect pancreatic islets and reduce hepatic steatosis and obesity on a high-fat diet. Preliminary data suggest that this class of drugs will be useful in obese T2DM patients.

Fatty acid-binding receptor (FABR) agonists trick the body into thinking you have just been to McDonalds

Fatty acids are part of an important nutrient signalling pathway which modulates the metabolic effects of food intake. FABR agonists use this strategy to 'trick' the body into thinking it has just eaten a fat-laden meal. The FABR responds to this perception of gastronomic gluttony by initiating a cascade of physiological events, including activation of the incretin system and secretion of insulin from the pancreas and leptin from the adipocytes.

Two FABRs are potential therapeutic targets, GPR40 and GPR120.[30] Both are deorphanized GPCRs with medium- and long-chain fatty acids as their ligands. GPR40 is of most interest since it is expressed on pancreatic β-cells and in the presence of glucose will amplify insulin secretion. A number of GPR40 agonists are currently being evaluated for T2DM therapy. One of these compounds, P-1736 (Piramal Life Sciences), is being tested in humans. One unresolved controversy, however, is whether GPR40 may also be responsible for the β-cell lipotoxicity produced by a chronic high-fat diet.

GPR120 is less well studied than GPR40. GPR120 is expressed in enteroendocrine cells which secrete GLP-1 and cholecystokinin. This receptor also has a role in adipogenesis and in inhibiting bone resorption. Further studies will be needed to define its role in T2DM, obesity and bone metabolism.

Anti-obesity therapies for 'diabesity'

The term 'diabesity' is a description for T2DM caused by excessive weight – the condition of having both diabetes and excessive weight. Many of the drugs that target obesity are antiglycaemic and benefit T2DM. We review some of these developing therapies.

Bariatric surgery

Bariatric surgery is unquestionably the most efficacious therapy for T2DM. Results show reductions in CVD, mortality, β-cell failure and glucose levels. In fact, the blood glucose normalizes in the majority of surgery patients for up to 2 years. Interestingly, the type of

procedure may make a difference. The Roux-en-Y gives better antiglycaemia results than gastric banding, perhaps because the Roux-en-Y expedites nutrient supply to the distal small intestine. This results in increased incretin secretion. Evidence for a possible incretin mechanism is that many patients become euglycaemic well before the weight loss. Furthermore, some of these patients go on to develop β-cell hyperplasia (nesidioblastosis), resulting in hyperinsulinaemic hypoglycaemia and requiring partial pancreatectomy. Further investigations on the mechanisms of bariatric surgery may lead to new therapeutic opportunities for T2DM.

Diacylglycerol acyltransferase (DGAT) inhibitors

DGAT catalyses the last step in triglyceride synthesis. When this enzyme is inhibited, body weight decreases due to increased energy expenditure, insulin levels decrease and hepatic steatosis is reduced. DGAT1 inhibitor studies have not been reported for T2DM, but the weight loss and increased insulin sensitivity are therapeutically promising.

11β-Hydroxysteroid dehydrogenase-1 (11BHSD) inhibitors

T2DM manifest many of the key features in Cushing syndrome, including adiposity, insulin resistance, dyslipidaemia and hypertension. 11BHSD converts inactive cortisone to cortisol in peripheral tissues and inhibition of this enzyme should reduce cellular cortisol activity. Therefore, 11BHSD inhibitors have been given to T2DM patients to examine the benefits of lowering cellular cortisol activity. To date, the theory has advanced beyond reality. The results so far show only a modest reduction in glucose with no other benefits. Further studies with other inhibitors are needed to evaluate this drug class fully.

Oxyntomodulin analogues with dual GLP-1 and glucagon activity

Oxyntomodulin is produced from the L-cells of the distal small bowel, the same cells that also produce GLP-1. This incretin combines GLP-1's antiglycaemia action and weight loss with glucagon's lipolytic activity and weight loss. GLP-1's glucose-lowering offsets the glucagon's hyperglycaemia and the weight loss benefits are additive. In order to augment oxyntomodulin's activity, pegylated forms have been produced to prolong stability and activity. Combinations of GLP-1 secretogogues and DPP4 inhibition, which promote the release and prolong the activity of oxyntomodulin, may also be pharmacological approaches.

Sterol-regulating element-binding protein inhibitor – fatostatin

Many of the lipogenic enzymes are encoded by genes regulated by sterol regulatory element-binding proteins (SREBPs). An inhibitor of these transcription, fatostatin, produces reductions in body weight, visceral adiposity and blood glucose in animals.

Endocannabinoid receptor (CB1) antagonists – may also prevent the 'marijuana munchies'

Endocannabinoid receptors bind both the psychoactive drug in marijuana (cannabis) and also endogenous ligands to produce a variety of physiological processes involved in memory, mood and appetite. Blocking the receptor suppresses appetite, producing reductions in body weight, lipids, blood pressure and glycaemia. Although one CB1 inhibitor (rimonabant) was initially approved for use in Europe, reports of severe depression led to withdrawal from the market and discontinuation of development. It is unlikely that other drugs in this class will continue development.

Lorcaserin (serotonin agonist) – Redux all over again?

Lorcaserin (APD-356) is a serotonergic weight-loss drug developed by Arena Pharmaceuticals that is pending drug approval by the FDA. A previous serotonergic agonist, dexfenfluramine (Redux), which was considered very efficacious, was taken off the market, however, because of its association with valvular cardiac lesions. Echocardiogram studies of lorcaserin users have not shown similar cardiac problems.

Anti-obesity combos – it takes two to tango

Pramlintide and metreleptin

Amylin and leptin are secreted from the pancreas and adipocytes, respectively, and they function as satiety signals resulting in reduced food intake and weight loss. Pramlintide and metreleptin are synthetic analogues and given in combination produce more weight loss than either given alone.

Contrave (naltrexone and bupropion)

Contrave is a combination of bupropion, a dopamine and noradrenaline reuptake inhibitor, with naltrexone, an opioid antagonist used to treat various addictive disorders. These two agents are reported to synergistically block β-endorphin-mediated inhibition of POMC (pro-opiomelanocortin) neurones, leading to increased hypothalamic anorexigenic neuronal activity. They have each on their own been shown to reduce appetite and body weight and these effects are additive when the two drugs are combined.

Qnexa (phentermine and topiramate)

Qnexa is a combination of low-dose phentermine and the anticonvulsant agent topiramate. Both drugs independently produce weight loss, and the effects are additive when the drugs are combined. In addition to weight loss,

lowering of blood pressure in hypertensives and antiglycaemia in T2DM patients have been reported.

Empatic (zonisamide and bupropion)
Empatic is almost like a cross between the two drugs mentioned above, Contrave and Qnexa, combining an anticonvulsant, zonisamide, and a dopamine/noradrenaline reuptake inhibitor, bupropion.

Conclusion

Given the recent explosion of T2DM in the USA, there is an urgent and tremendous need for improved antiglycaemic therapies for T2DM. Current therapies lack the ability to stop the progression of this disease or its macrovascular complications and mortality. Newer therapies will need to do more than just lower glucose. Many of the new and emerging drugs, especially in the incretin class, appear to have positive β-cell and cardiac benefits. Time will tell, however, since in the past other classes of diabetic therapies have promised but failed to deliver.

Key points

- Numerous new drugs for the treatment of diabetes are being developed.
- Anti-obesity drugs have so far been minimally effective.
- Avoidance of hypoglycaemia is a key issue in older persons.

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SECTION 11

Urogenital Disorders

CHAPTER 103

Gynaecology and the older patient[1]

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Introduction

The ageing population presents a major challenge for the society and the health services worldwide. It is a reflection of longer life expectancy because of improvements in living standards and healthcare and falling mortality. In the United Kingdom, people aged 60 and above had outnumbered children under 16 (21% compared to 20%). By 2026, nearly 28% of the UK population will be over the age of 60.[2] Women constitute a majority of the elderly population as they outlive males by 5–7 years. Sixty-five years is the accepted starting point of old age, that is, the official retirement age (at time of writing) in the Western world. Female ageing is unique in that it represents a combination of the ageing processes and hormone deficiency. This chapter reviews the problems of the old-age gynaecology patient with reference to the common symptomatology, the menopause, hormone replacement therapy, sexuality and malignancies.

Effect of ageing on the genital tract

Vulva and vagina

The lower genital tract undergoes atrophic changes with loss of connective tissue elasticity and thinning of the mucosa. There is a decline in intracellular glycogen production in the vagina, leading to a decrease in lactobacillae and lactic acid and an increase in the vaginal pH from acid to alkaline. These changes lead to an increase in colonization by pathogenic bacteria and infective vaginitis. Senile or atrophic vaginitis is also common due to loss of vaginal tissue elasticity and shrinkage of the vagina with subsequent loss of lubrication. This can lead to postmenopausal bleeding and dyspareunia.

Cervix and uterus

The cervix becomes atrophic and the ectocervix becomes flush with the vaginal vault. The squamocolumnar junction of the cervix recedes into the endocervical canal and it becomes difficult to obtain an accurate representative cervical smear. The uterus undergoes atrophy of myometrium and the uterine body becomes smaller. The endometrium becomes thinner and the glands become inactive.

Ovary and fallopian tube

In the perimenopausal years, the few remaining primordial follicles become unresponsive to the pituitary gonadotrophins and therefore the estrogen secretion falls. The ovaries become smaller and more wrinkled in appearance. The fallopian tubes become shorter with muscle replaced by fibrous tissue.

Pelvic floor

Pelvic floor muscle weakness is due to the combined effects of estrogen withdrawal and age. This is compounded by the mechanical effects of previous childbirth. The endopelvic fascia surrounding both the genital tract and urinary tract atrophies. The fascial condensations of cardinal and uterosacral ligaments also atrophy, leading to an increased incidence of genital prolapse as age increases. In the elderly, chronic cough, constipation and increased intra-abdominal pressure are other factors contributing to this.

Urethra and bladder

Both the urethra and trigone of the bladder are sensitive to estrogen as they have estrogen receptors and there is deterioration in structure and function as a woman ages.

[1]This chapter is based in part on the chapter 'Gynaecology' by Jarmila Wiener and Joan Andrews, which appeared in *Principles and Practice of Geriatric Medicine*, 3rd Edition.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

The urethral lumen becomes more slit shaped and the folds become coarser. The mucosal lining changes from transitional in the proximal two-thirds to non-keratinizing squamous epithelium.[2] Urethral closure becomes less competent. There is a reduction in detrusor contraction power during voiding and the contractions fade shortly after initiation of voiding. Bladder capacity is also reduced in the elderly. All these features contribute to the greater prevalence of urinary incontinence in elderly women. Estrogen withdrawal may also lead to a high prevalence of urinary tract infection in the elderly, which is aggravated by voiding difficulty and may lead to stress incontinence, urge incontinence, frequency, urgency and nocturia.[3]

Hormonal changes

In premenopausal women, ovarian function is controlled by the two pituitary gonadotrophins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). These are controlled by the pulsastile secretion of gonadotrophin releasing hormone (GnRH) from the hypothalamus. The ovary has the maximum number of oocytes at 20–28weeks of intrauterine life. There is a reduction in these cells from midgestation onwards and the oocyte stock becomes exhausted in the perimenopausal age group. The ovary gradually becomes less responsive to gonadotrophins resulting in a gradual increase in FSH and LH levels, and a fall in estradiol concentration. As ovarian unresponsiveness becomes more marked, cycles tend to become anovulatory and complete failure of follicular development occurs. Estradiol production from the granulosa and theca cells of the ovary ceases and there is insufficient estradiol to stimulate the endometrium; amenorrhoea ensues. FSH and LH levels are persistently elevated. FSH level >30 IU l^{-1} is generally considered to be the postmenopausal range

The menopause and HRT (hormone replacement therapy)

Menopause is defined as the permanent cessation of menstruation. The word menopause is derived from the Greek words *menos* (the month) and *pausos* (ending). It is a retrospective diagnosis since a woman is menopausal only after 12 months of amenorrhoea. The average age of menopause is 51 years and the female life expectancy is now over 80 years. Postmenopausal women spend more than 30 years in a profound estrogen-deficient state. The early symptoms of menopause are vasomotor symptoms, principally hot flushes, night sweats and insomnia. The long-term consequences are osteoporosis, urogenital atrophy, cardiovascular disease and connective tissue atrophy.

Vasomotor symptoms

There is good evidence from randomized placebo-controlled studies that estrogen is effective in treating hot flushes and improvement is noted within four weeks.[4] Relief of vasomotor symptoms is the commonest indication for HRT and current recommendations for the duration of use is for up to five years. In general, as old age approaches, the symptoms of the menopause appear to resolve spontaneously, though of course, the risk of osteoporosis increases. However, there are a small proportion of women whose menopausal symptoms (hot flushes in particular) last well into later life. Since non-hormonal treatments for hot flushes are universally ineffective management of this group can be a challenging problem. There is subsequently a small group of women who request HRT well beyond the five years normally recommended.

Osteoporosis

Osteoporosis has been defined by the World Health Organization (WHO) as a 'disease characterized by low bone mass and micro-architectural deterioration of bone tissues, leading to enhanced bone fragility and a consequent increase in fracture risk'. In postmenopausal women, there is accelerated bone loss, so that by the age of 70 years, 50% of bone mass is lost. The risk factors for osteoporosis include family history, low BMI, cigarette smoking, alcohol abuse, early menopause, sedentary lifestyle, corticosteroids. Fractures are the clinical consequences of osteoporosis. The most common sites of osteoporotic fractures are the distal forearm (wrist or Colles fracture), proximal femur and vertebrae. Vertebral fractures lead to loss of height and curvature of the spine with typical dorsal kyphosis ('Dowager's hump'). This affects their overall QOL and may ultimately impair respiratory function. There is evidence from randomized controlled trials that HRT reduces the risk of osteoporotic fractures.[5,6] However, recent advice from regulatory authorities has been that HRT should not be used for osteoporosis prevention as the risks of such treatment outweigh the benefits.[7] After the publication of the Million Women study in 2003, the Committee on Safety of Medicines (CSM) pronounced that HRT was no longer to be considered as first-line therapy for the prevention of osteoporosis. Bisphosphonates may be the best choice for the over 60s, though there is actually less data on long-term safety.

Urogenital symptoms

Symptoms such as vaginal dryness, soreness, superficial dyspareunia and urinary frequency and urgency respond well to local estrogen, in the form of pessaries, rings and

tablets. Estradiol tablets (Vagifem® Novo Nordisk) are associated with minimal or no systemic absorption. In light of this it is believed that long-term use of Vagifem is safe in contrast with other vaginal estradiol preparations. However, there is currently no clear evidence to support its long-term safety,

Risks of HRT

Breast cancer

HRT appears to confer a similar degree of risk as that associated with late natural menopause. In absolute terms, the excess risk in the Women's Health Initiative (WHI) study with continuous combined HRT at 50–59 years was 5; 60–69 years, 8; and 70–79 years, 13 cases of breast cancer per 10 000 women per year.[8] The unopposed estrogen-only arm of this study did not show any evidence of an excess increase in breast cancer risk. The Million Women study found an increased risk with all HRT regimens, the greatest degree of risk was with combined HRT.[9] So the addition of progestogen increases breast cancer risk compared with estrogen alone but this has to be balanced against the reduction in risk of endometrial cancer provided by combined therapy.[8,10] Irrespective of the type of HRT prescribed, breast cancer risk falls after cessation of use, risk being no greater than that in women who have never been exposed to HRT by five years.

Endometrial cancer

Unopposed estrogen replacement therapy increases endometrial cancer risk. Most studies have shown that this excess risk is not completely eliminated with monthly sequential progestogen addition especially when continued for more than five years. No increase has been found with continuous combined regimens.[11] Administration of the progestogen by the intrauterine route (Mirena® (levanorgestrol-releasing system)) would seem to have the benefit of maximal endometrial dose with low systemic effects.

Venous thromboembolism

HRT increases risk of venous thromboembolism (VTE) twofold with the highest risk occurring in the first year of use. Advancing age and obesity significantly increase this risk. The absolute rate increase is 1.5 VTE events per 10 000 women in one year. This risk is lower with transdermal estradiol compared to oral due to avoiding the first pass metabolism effect in the hepatic circulation.

Cardiovascular disease (coronary heart disease and stroke)

The role of HRT either in primary or secondary prevention of cardiovascular disease remains uncertain and so it should not be used primarily for this indication. The WHI study showed an early transient increase in coronary events. The excess absolute risk at 50–59 years was 4; 60–69 years, 9; and 70–79 years, 13 cases of stroke per 10 000 women per year. However, the timing, dose, and possibly type of HRT may be crucial in determining cardiovascular effects. In hypertensive patients it is recommended that once the blood pressure is under control estrogen can be given. Therefore, HRT should currently not be prescribed solely for possible prevention of cardiovascular disease. The merits of long-term use of HRT need to be assessed for each woman at regular intervals. It should be targeted to the individual woman's needs.

Alzheimer's disease

While estrogen may delay or reduce the risk of Alzheimer's disease, it does not seem to improve established disease. WHI study found a twofold increased risk of dementia in women receiving the particular combined estrogen and progestogen regimen. However, this risk was only significant in the group of women over 75 years of age. More evidence is required before definitive advice can be given in relation to Alzheimer's disease.

Common symptoms in the elderly

Older women are often reluctant to approach their practitioners due to embarrassment when they suffer from the symptoms as in Table 103.1.

Postmenopausal bleeding (PMB)

Postmenopausal bleeding is defined as bleeding from the genital tract after one year of amenorrhoea. A woman not taking HRT who bleeds after the menopause has a 10% risk of having a genital cancer'.[12] In the vast majority of cases, the cause is benign, mainly atrophic vaginitis. The causes are as in Table 103.2.

Diagnosis

History should include the symptoms, drug history and smear history. Assessment may be difficult in an elderly patient and is frequently complicated by dementia, immobility, obesity and arthritis. A thorough examination including BMI, abdominal examination for masses, pelvic examination including speculum and bimanual examination should be carried out.

Investigation

The principal aim of investigation is to exclude the possibility of cancer. Transvaginal ultrasound measurement

Table 103.1 Common symptoms in the elderly.

Postmenopausal bleeding
Discharge per vagina
Pelvic mass
Prolapse
Urinary incontinence
Vulval soreness or itching
Vulval pain
Vulval swelling

Table 103.2 Causes of postmenopausal bleeding.

Atrophic – Senile vaginitis
Decubitus ulcer from a prolapse
Neoplasia – Endometrial cancer
Cervical cancer, vaginal cancer
Vulval cancer, estrogen-secreting tumours, ovarian tumours
Fallopian tube cancer, secondary deposits
Endometrial polyps
Iatrogenic – Bleeding on HRT
Bleeding on tamoxifen
Local ulceration due to Ring, shelf pessary
Infection – Vaginal, endometrial
Others – Haematuria, rectal bleeding, trauma, foreign body

of endometrial thickness will help in directing the need for an endometrial biopsy. An endometrial thickness of less than 5 mm is reassuring that the cavity is empty. The myometrium and ovaries can also be visualized for evidence of tumours. Hysteroscopy and endometrial biopsy is now the 'gold standard' investigation for postmenopausal bleeding. Increasingly this procedure is carried out under local anaesthetic in the outpatient setting. In some cases technical difficulties such as cervical stenosis associated with atrophic change may require a general anaesthetic. A full assessment will include cystoscopy and sigmoidoscopy if there is any doubt concerning the source of the bleeding.

Treatment

Treatment depends on the cause of the bleeding. If atrophic vaginitis is diagnosed treatment is by local estrogen therapy. Where ulceration is caused by a pessary, removal of the pessary until the area has healed is the correct course of action. A course of vaginal estrogen is often helpful in preventing further ulceration. In cases of procidenta with decubitus ulceration the woman may have to be admitted to hospital for vaginal estrogen packs and urinary catheterization. Where a malignancy is suspected or diagnosed management is in a multidisciplinary forum in accordance with local and national Cancer Network Guidelines.

Table 103.3 Causes of discharge per vagina.

Atrophic – Postmenopausal vaginitis
Infective – Bacterial vaginosis, trichomoniasis, Chlamydia, gonorrhoea
Tumours – Cervical polyp, intrauterine polyp
Cervical cancer, endometrial cancer,
Fallopian tube cancer – rare
Fistulae – Vesicovaginal fistula, rectovaginal fistula
Pyometra – associated with carcinoma of the endometrium
Others – foreign body, pessary

Discharge per vagina

Vaginal discharge is a common gynaecological complaint seen in the elderly. The causes are as in Table 103.3. Owing to the loss of vaginal tissue elasticity and shrinkage of the vagina, atrophic vaginitis is very common. Infective vaginitis is also common due to colonization by pathogenic bacteria when the vaginal pH shifts from acid to alkali. In addition sexually transmitted infections are increasing in prevalence in the older population.

Uterovaginal prolapse

Uterovaginal prolapse is a herniation of the female genital tract. It is extremely common with an estimated 11% of women undergoing at least one operation for this condition. The aetiology is multifactorial but the principle factors responsible for the development of prolapse are damage occurring during pregnancy and childbirth along with weakening of fascia and muscle support following the menopause. Raised intra-abdominal pressure due to obesity, chronic constipation or cough is also a major contributory factor. Finally loss of suspensory support following hysterectomy or a congenital predisposition are other significant causes of prolapse. Due to a shared aetiology uterovaginal prolapse is commonly associated with urinary incontinence.

Classification

1 Anterior vaginal wall prolapse
- **i** Urethrocele – Urethral descent
- **ii** Cystocele – Bladder descent
- **iii** Cystourethrocele – Descent of bladder and urethra

2 Posterior vaginal wall prolapse
- **i** Rectocele – Rectal descent
- **ii** Enterocele – Small bowel descent

3 Apical vaginal prolapse
- **i** Uterovaginal – Uterine descent with inversion of vaginal apex
- **ii** Vault – Post hysterectomy inversion of vaginal apex

Diagnosis

Most commonly, the presenting symptom is a feeling of a lump coming down the vagina. Women also present with a dragging or bearing down sensation of gradual onset which is worse with activity and settles with rest. A minor prolapse may become symptomatic in the presence of marked atrophic vaginitis. Atrophic ulceration may occur with discharge and bleeding. Urinary symptoms such as frequency, urgency, incontinence, incomplete, or slow emptying result from distortion of the prolapsed bladder and urethra. Digital replacement of the anterior or posterior vaginal wall is sometimes necessary before micturition or defecation respectively.

A detailed obstetric history to identify causative factors and a comprehensive medical history to assess comorbidities, which may have an aetiological role such as constipation or cough, is essential. A detailed social history to assess QOL must be taken and most importantly a sexual history to assess the desire for future sexual function is central to planning management.

General examination: To assess if surgery is safe, to check BMI, and cardio-respiratory system examination.

Abdominal examination: Looking for pelvic masses.

Pelvic examination: Prolapse may be obvious when examining the patient in the dorsal position if it protrudes beyond the introitus, ulceration and/or atrophy may be apparent. The anterior and posterior vaginal walls and cervical descent should be assessed with the patient in the left lateral position, using a firm Sims speculum. Combined rectal and vaginal digital examination can be an aid to differentiate rectocele from enterocele. Vaginal examination should be performed and pelvic mass excluded. Urine culture and sensitivity, cystometry and cystoscopy to be considered when symptoms include both stress and urge incontinence and especially prior to consideration of surgery.

Management

The management of prolapse depends on the severity of symptoms, the degree of incapacity and the patient's operative fitness. Operative treatment by repair of prolapse with or without vaginal hysterectomy is most effective. Obesity, heavy smoking and constipation require improvement before surgery. Most patients tolerate surgery very well because of improved anaesthetics and minimal postoperative morbidity. When such surgery is undertaken in an older woman, it is important to ascertain the level of sexual activity as this will influence the degree of narrowing achieved by surgery. Age *per se* is not a contraindication to surgery. Medical disorders develop with advanced age and these dictate any reasons for avoiding anaesthesia.

When surgery is contraindicated or declined, conservative methods may be used. A polyvinyl ring pessary will be successful, providing there is adequate perineum to retain the pessary. Some patients, particularly those with large prolapses and very little perineum, may do better with a shelf pessary. Either type needs changing at 4–6 month intervals and the vagina should be inspected to ensure no ulceration has occurred. If ulceration occurs, the pessary should be removed for a few weeks and local estrogen used daily to allow epithelial healing.

Physiotherapy: Pelvic floor exercises are useful for the prevention and improvement of incontinence. But they require good patient motivation. Physiotherapy may improve symptoms from a small prolapse but it is unlikely to help with a greater degree of herniation.

Urinary incontinence

Urinary incontinence is defined as the involuntary loss of urine that is objectively demonstrable and is a social or hygiene problem. The causes are as in Table 103.4. The prevalence increases with age, with approximately 10% of those aged between 45 and 64 years of age being affected, rising to 20% of those greater than 65 years. It is even higher in women who are institutionalized and may affect up to 40% of those in residential nursing homes. This places huge financial demands on health resources, with 2% of the total budget being spent on incontinence services alone. Many women will not seek advice because of embarrassment.

Uninhibited detrusor muscle contractions are usually the cause in geriatric patients owing to age-related changes in the central nervous system. Genuine stress incontinence (GSI) occurs when the bladder pressure exceeds the maximum urethral pressure in the absence of any detrusor contraction and this is common in the early postmenopausal years. In many women, the two conditions exist together.

Assessment

A good history will help to differentiate GSI from detrusor instability to some extent. Examination to rule out any associated prolapse or pelvic mass should be carried out in

Table 103.4 Causes of urinary incontinence.

1	Genuine/urodynamic stress incontinence – Bladder neck hypermobility, urethral sphincter weakness
2	Detrusor instability – Idiopathic, secondary to neurological disease – hyperreflexia
3	Retention with overflow – Motor neurone lesions, drugs, pelvic mass, severe prolapse
4	Fistulae – Ureteric, vesical, urethral
5	Miscellaneous – Urinary infection

these patients. Urodynamic studies are necessary to confirm the diagnosis, especially prior to any surgical treatment.

Management

Simple measures like exclusion of urinary tract infection, restriction of fluid intake, modifying medication like diuretics when possible, play an important role in the management of urinary incontinence.

Genuine stress incontinence (GSI)

Conservative management: The treatment of GSI should be non-operative initially, and the best results for mild/moderate leakage are with pelvic floor exercises. The rationale behind pelvic floor education is the reinforcement of cortical awareness of the levator ani muscle group, hypertrophy of existing fibres and a general increase in muscle tone and strength. Motivation and good compliance are the key factors associated with success. Local estrogen therapy may have a small effect by improving the urethral mucosa in women with estrogen deficiency.

Surgical management – the aims of surgery:

- Restoration of the proximal urethra and bladder neck to the zone of intra-abdominal pressure transmission
- To increase urethral resistance.

The procedures are vaginal tapes (TVT, TOT), periurethral bulking using collagen, macroplastique.

Detrusor instability (DI)

DI can be treated by bladder retraining and biofeedback, all of which tend to increase the interval between voids and inhibit the symptoms of urgency. Drug treatment is mainly by anticholinergics like oxybutynin, tolteridine, regurin combined with local estrogen.

Sexuality and old age

In the past, it was mistakenly assumed that a woman well past the menopause will not be sexually active. In 1953, Kinsey *et al*. described reduced sexual activity in elderly women. In this group of women, orgasm was more likely to be achieved by masturbation than by coitus.[13] In fact, sexual drive is not exhausted with ageing, and as life expectancy increases it is necessary to recognize that continued sexual activity is an important requirement to promote satisfactory relationships, personal well-being and QOL.[14] Many older people grew up in sexually restricted times so that ignorance is widespread. The organization of institutions for elderly people does not recognize their sexuality, so their needs are ignored.[15] It has been proved that sexual activity remains relatively constant within a stable relationship and declines only following death or illness of the partner.[16]

Sexual response and ageing

In the elderly, the changes of vasocongestion, pudendal swelling and vaginal lubrication are reduced and delayed, and resolution occurs more rapidly. Also, vaginal lubrication diminishes and there is less vaginal elasticity leading to shrinkage of the vagina. Coital trauma to the vagina and urethra causes dyspareunia, dysuria and postmenopausal bleeding. Lesions of the vulva like lichen sclerosus (LS) and surgical scarring may make intercourse impossible for some older women.

Health factors that inhibit sexual activity in elderly people

Physical factors

- Stress incontinence
- Diminishing mobility
- Decreasing muscle tone
- Uterine prolapse
- Skin tone and sensitivity
- Diseases like diabetes and cardiovascular problems
- Chronic conditions like arthritis.

Psychological factors

- Sense of unattractiveness
- Facing mortality; depression, bereavement and grief reactions
- Loss of partner or friends
- Lack of contact with others and loneliness.

Effect of chronic illness and surgery on sexuality

Chronic urological and gynaecological conditions causing pain on intercourse, chronic anxiety and stress, neurological disorders, depression and fatigue can result in loss of sexual desire. Disfiguring and mutilating operations, especially of the breasts, genitals and reproductive organs, often have a deleterious effect on a woman's self image and sexuality. Dyspareunia can be a major problem, not only because of lack of arousal or secondary vaginismus after surgery but also because of the amount of scar tissue within the pelvis. Women who have a stoma-like colostomy or ileostomy also experience psychological problems. Patients' greatest fears are loss of control, bad odour, noise, leaking bags and their partner's feelings toward them. Healthy adaptation to a stoma depends on preoperative and postoperative counselling and understanding by stoma nurses.

Management

A detailed sexual history including the problem, the duration, the couple's past life together and emotional

relationship should be taken. Early experiences, difficulties with a previous partner and any episode of sexual assault is also important. Examination should aim to look for a physical cause of the sexual problem. Behavioural techniques play an important part in the management of sexual dysfunction. Ignorance about sexuality is common. Changing negative attitudes resulting from past experiences, parental or religious influences will help. Talking to each other about sexual anxieties or needs, and discussion with a therapist increases their mutual understanding and ability to communicate.

Psychological therapy

The psychological approaches include giving accurate information, general counselling, psychosexual therapy, behavioural therapy, sexual and relationship therapy. Before any operation, it is essential to discuss with the woman, preferably with her partner, the full implications of the operation on their sexual life. This helps to minimize sexual dysfunction after the operation.

Pharmacological therapy

There is now evidence from randomized controlled studies that testosterone therapy improves sexual satisfaction and mood in surgically menopausal women treated with concurrent estrogen.[17,18] However, long-term safety data for combined estrogen-testosterone therapy are lacking, and the effects of testosterone-only therapy on such factors as plasma lipids in postmenopausal women are unknown.

The use of appropriate creams to help with vaginal soreness – such as vaginal estrogen, KY Jelly, Sylk or aromatic oils may enable a woman and her partner to enjoy sexual activity much more fully.

Vulval disorders

As the lower genital tract undergoes atrophic changes, the labia majora lose their fat and elastic tissue content and become smaller. The vulval epithelium becomes thin, leading to vulval irritation. Other symptoms are itching and soreness. The conditions affecting the vulva can be a part of a more widespread problem, such as psoriasis or conditions specific to the vulva. Vulval disorders are important because of the chronicity and severity of symptoms and the association with carcinoma. The common benign vulval disorders are as follows:

1 Lichen sclerosus
2 Squamous cell hyperplasia
3 Other dematoses
4 Vulvodynia or chronic vulval pain.

Lichen sclerosus (LS)

LS is a chronic skin condition characterized by the thinning of the epithelium with loss of keratin which frequently extends around the anus. The aetiology is uncertain, but there is an association with genetic and hormonal factors and autoimmune disease.[19] The clinical signs include pale ivory white plaques often with a crinkly atrophic surface, purpura and scarring with gradual destruction of the normal vulval architecture. Complications include narrowing of the introitus and rarely squamous cell carcinoma. Punch biopsies should be taken of any suspicious areas. Squamous cell carcinoma is more likely when there is ulceration, raised lesions or lymph node involvement. The most effective treatment is to use topical steroid ointment clobetasol propionate 0.05% plus a soap substitute.

Squamous cell hyperplasia

The skin is usually reddened with exaggerated folds. In certain areas, after rubbing, lichenification can be seen. The term squamous cell hyperplasia is applied for those women who have histological evidence for the cause.

Other dermatoses

The most common general diseases causing vulval itching or discomfort are diabetes, uraemia and liver failure. Other causes are allergic dermatitis caused by irritants such as perfumed soap, washing powder and so on. General dermatological conditions such as psoriasis, lichen planus and scabies may also affect the vulva.

Vulvodynia (vulval pain)

Vulvodynia is defined as chronic pain, discomfort or burning in the absence of a relevant skin condition. This condition is common in elderly women. The aetiology is uncertain but psychological and physical factors play a role. Depression is also a compounding factor. Treatment initially is empirical using topical steroids, anaesthetic and estrogen cream. The use of antidepressants and antiepileptic therapy should be considered for its analgesic effects. A multidisciplinary approach involving specialists in dermatology, pain relief, psychiatry and gynaecology is essential for intractable cases.

Gynaecological cancer

The most common types of gynaecological malignancies are cervical cancer, ovarian cancer, endometrial cancer and vulval cancer. Occasionally, skin cancers or sarcomas can also be found in the female genitalia.

Cervical cancer

Worldwide, cervical cancer is the most common gynaecological malignancy. The aetiological factors include multiple sexual partners, early age of coitus, human papilloma virus (HPV) 16 and 18 infection. In developed countries, there is an overall decline in incidence and mortality from cervical cancer as a result of the cervical screening programme. There is a defined premalignant stage, namely, cervical intraepithelial neoplasia – CIN1, CIN2 and CIN3. Screening for cervical cancer is by cervical smear. Liquid-based cytology and HPV testing are new developments taking place in this field. Abnormal cytological findings are an indication for further investigation by colposcopy and if necessary, directed biopsies or excision biopsy.

Approximately 500 000 new cases of cervical cancer are diagnosed each year in the world with 80% of these occurring in the less developed world.[20] More than 80% of cervical cancers are squamous cell carcinomas. The presenting symptoms are postcoital bleeding, vaginal discharge, or postmenopausal bleeding. Pain is experienced late and is due to pelvic infiltration or bony metastases. The first sign of this cancer may be obstructive renal failure from hydronephrosis due to advanced disease. On inspection, cancer of the cervix presents as an ulcer, growth, or a friable warty looking mass which bleeds on touch. As the carcinoma progresses, the mobility of the cervix is affected and the cervix eventually becomes fixed. Diagnosis is by biopsy of suspicious areas, preferably under general anaesthesia so that clinical staging can be done. Treatment for clinical invasive carcinoma of the cervix is by surgery, chemo-radiotherapy or a combination of all three. The management of gynaecological cancer patients is now mostly centralized in units staffed by gynaecological oncologists, so that all the treatment modalities can be offered to patients. In early disease confined to the cervix, then either surgery or radiotherapy may be offered since the prognosis is equally good for both. Surgery is by radical hysterectomy and pelvic node dissection, that is, Wertheim's hysterectomy. In the elderly, radiotherapy is usually offered because of the fear of surgical complications. However, a fit patient will tolerate the procedure well and age by itself should be no bar to surgery. If the disease is in a late stage, then chemo-radiotherapy is the treatment of choice. In an unfit patient with advanced disease, palliative care may be the only option.

Endometrial cancer

Carcinoma of the endometrium is considered as the gynaecological cancer with a relatively favourable prognosis because of its early presentation with postmenopausal bleeding. The median age of patients with endometrial cancer is 61 years, with 80% of women being postmenopausal. The risk factors are obesity, diabetes mellitus, hypertension, nulliparity, late menopause, unopposed estrogen therapy and prior history of polycystic ovary syndrome. The presenting symptom in the elderly is almost always postmenopausal bleeding. Late diagnosis includes pain and discharge from a pyometra. The diagnosis is by transvaginal ultrasound determination of endometrial thickness and endometrial biopsy. Outpatient hysteroscopy also may be undertaken, but if there is cervical stenosis, then hysteroscopy should be done under general anaesthesia. Early disease is treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy. In a poorly differentiated tumour or if the myometrium is involved beyond the inner third, postoperative radiotherapy is given. Advanced cancers are treated with radiotherapy. Progestational agents are used for recurrent disease to control vaginal bleeding and to reduce the pain from bony metastases.

Ovarian cancer

Carcinoma of the ovary is common in developed countries. The peak incidence is in the 50–70 year age group. Ovarian cancer remains the most lethal gynaecological malignancy despite trials of many different treatment regimens to try to improve the poor prognosis. Most women present with advanced disease. There is no satisfactory screening method for ovarian neoplasia, but women with a family history of breast or ovarian cancer should be offered regular ultrasonic assessment and measurement of the tumour marker, Ca 125. This test is not sensitive or specific enough to be applied to the general population.

Ninety percent of ovarian carcinomas in older women are epithelial adenocarcinomas, but sex cord and germ cell tumours may also be seen in this age group. Also, metastases may be seen from elsewhere, particularly colon and breast. Granulosa cell tumour is the most common sex cord tumour. This produces estrogen which can cause postmenopausal bleeding due to the resulting endometrial hyperplasia.

The presenting symptoms are often vague including abdominal discomfort, swelling, malaise and weight loss. Later symptoms include abdominal pain and distension, ascites and pleural effusion. Investigations include haematological, biochemical, imaging techniques like ultrasound and CT scan. Solid areas within an ovarian cyst and ascites are strongly suggestive of malignancy. The final diagnosis is by laparotomy.

Management

The mainstay of treatment is by debulking of the tumour with bilateral salpingo-oophorectomy, total hysterectomy and omentectomy. Postoperative chemotherapy is used in

all but early stages and indeed many patients will have residual disease after surgery. Radiotherapy is limited to patients with symptomatic recurrence and is used only for palliation.

Vulval cancer

Vulval cancer is a less common cancer and is most frequently seen in the 60–70 year age group. The presenting symptoms are soreness, pruritus, irritation, ulceration, lump, or bleeding. Many women present very late because of embarrassment. Ninety-five percent of vulval carcinomas are squamous cell carcinomas, but basal cell carcinoma, malignant melanoma and adenocarcinoma of the Bartholin's gland may occur rarely. Diagnosis can be confirmed only by vulval biopsy.

Management

Radical vulvectomy with bilateral groin node dissection is the treatment of choice. The common complications are wound breakdown and infection. The primary tumour is resected and separate groin node dissections are performed to improve wound healing and reduce infection. The other complications are deep vein thrombosis, osteitis pubis, secondary haemorrhage and so on. For patients unfit for surgery, wide excision of the lesion may be used as palliation. Pelvic irradiation is available for extensive nodal involvement.

HIV and old age

The majority of those infected and affected by HIV are younger adults. The ability of highly active antiretroviral therapies (HAART) to extend survival means that those infected when younger may reach older age and so an increase in numbers of older individuals living with HIV is expected. There is evidence that older individuals engage in risky sexual behaviours and are drug users, suggesting potential for HIV transmission.[21] For older women after menopause, condom use becomes unimportant, and normal ageing changes such as a decrease in vaginal lubrication and thinning vaginal walls can put them at higher risk during unprotected sexual intercourse.

Key points

Doctors often do not consider the possibility of HIV/AIDS in older patients because they do not perceive them to be at risk or they presume symptoms to be age related. As a result, many older people are diagnosed at a later stage in their infection, and many have an AIDS diagnosis the first time they become aware of their HIV infection. Older people are more likely to be diagnosed with HIV at a generally higher viral load and lower CD4+ cell count, making them more susceptible to opportunistic infections. More aggressive therapy may be required to successfully suppress the virus.

Data from the Centers for Disease Control (CDC) HIV/AIDS surveillance report showed that 11% of all AIDS cases reported in 1999 were among people aged 50 and above.[22] This percentage has remained stable since 1991. However, the CDC notes an alarming trend in that older AIDS patients had a greater increase in opportunistic infections than did younger AIDS patients. The report also says a higher proportion of people aged 50 and above died within one month of AIDS diagnosis. These deaths can be attributed to original misdiagnosis and immune systems that naturally weaken with age. These statistics seem to confirm the idea that older adults are naive about their risk of contracting HIV and their providers are not discussing that risk with them. A 1997 study of Texas doctors found that most physicians rarely or never discussed HIV and risk factors with their older patients.[23] Compounding the problem, AIDS symptoms often are more difficult to diagnose in older people because they mimic some common diseases associated with old age. Because of the stigma, it can be difficult for women to disclose their HIV status to family, friends and their community.

For these reasons, physicians should keep HIV in mind as a possibility, even with their older patients. HIV experts recommend that physicians routinely ask all patients about their sexual behaviour during the annual physical or gynaecological examination. Providers should educate the population over 50 years about possible exposures to HIV and safer sex practices.

Conclusion

Gynaecology for the elderly patient includes the whole spectrum of gynaecological disorders of which cancer, prolapse, urinary incontinence and the problems of late menopause are the most important ones. The advice given for such women changes with each decade. Of particular note is our increasing reluctance to give long-term HRT and our increasing likelihood of undertaking surgery in women who are healthy despite their age. Many women, through fear and embarrassment, avoid telling their problems to general practitioners, geriatricians, or gynaecologists and so present with long-standing disease.

Key points

- The female ageing process is unique in that it represents a combination of the ageing processes and hormone deficiency.

- Managing the menopause should be targeted to individual women's needs. The benefit of hormone replacement often outweighs the risks, provided the appropriate regimen has been instigated in terms of dose, route and combination.
- Age *per se* should not be a contraindication to surgical management for any gynaecological problem.
- There is no age limit for the expression of sexuality. The management of sexual problems should be guided by the same principles irrespective of age and condition of the patient.
- Older women, out of fear and embarrassment, neglect early symptoms of gynaecological diseases, some of which are potentially lethal.

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CHAPTER 104

The ageing bladder

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Introduction

The increase in human life expectancy unmasked a variety of genitourinary complaints. Most physicians are familiar with lower urinary tract symptoms suffered by the ageing male related to prostatic enlargement. Equally debilitating though are bladder symptoms found in both sexes totally unrelated to obstruction of any kind. Symptoms of frequency, urgency and urge incontinence, commonly lumped together under the term 'overactive bladder' are very prevalent in the ageing patient and confront the physicians who care for them on a daily basis.

A multitude of other influences on the bladder also exist that affect its performance over a lifetime. Certainly injury from infection or surgery can affect vesical function over both long- and short-term horizons. Changes in the bladder outlet via prostatic obstruction in males or overzealous surgery in women can have effects ranging from mild to devastating on detrusor function. Alterations in the neurological milieu of the lower urinary tract can profoundly alter bladder function. These variations, when severe enough, can not only create difficult symptomatology for the patient but also occasionally be detrimental to renal function.

In this chapter, we examine the ageing bladder from a number of angles. The alterations in vesical anatomy both gross and microscopic are important in dysfunctional voiding and incontinence associated with ageing. Neuronal and hormonal changes influence the ageing bladder. Pharmaceutical agents are under intense scrutiny as to their effect in urinary tract as well as their side effects in the elderly patient. Finally, special disease states found mostly in the older population have specific effects on the urinary tract that must be considered in the overall therapy for those diseases.

Anatomy of the ageing bladder

The normal bladder is characterized grossly by its pelvic position in the adult. In the older male, the macroscopic anatomy of the bladder is most commonly affected by the growth of the prostate gland. Although most commonly benign prostate growth occurs in the transition zone surrounding the urethra, occasionally this growth becomes unrestrained in a cephalad manner and pushes the trigone superiorly to give the bladder an elevated appearance radiographically. Gross inspection of the bladder interior often demonstrates a trabeculated appearance. Trabeculations are often thought to be a sign of chronic obstruction but have also been observed in the female bladder as well.[1]

In women, the anatomical position of the bladder is most often altered by defects in the pelvic floor musculature. This leads to the presentation of cystoceles, effectively a herniation of the bladder through the anterior vaginal muscle layers. This defect, as well as rectoceles and enteroceles are commonly noted in parous individuals although the impact of ageing, obesity and possibly neurological dysfunction can be substantial.[2,3] Perucchini has demonstrated localized striated urethral muscle loss with ageing at the bladder neck and dorsal wall of the urethra.[4] Others have shown an increase in paraurethral connective tissue in elderly females with a reduction of blood vessels.[5] Falconer has demonstrated that altered collagen production in women with stress incontinence and poor quality collagen seen in postmenopausal women possibly contribute to disorders related to prolapse in the elderly.[6]

The histologic appearance of the ageing bladder can give clues to its ultimate ability to function as a storage facility for urine. Ultrastructural changes in the ageing bladder include collagen deposition, muscle degeneration and axonal degeneration. The degree of these changes

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may correlate with specific abnormalities in voiding and incontinence such as detrusor overactivity and impaired contractility.[7] Chronic ischaemia of the bladder may play a large causative role in these changes.[8]

Surgical procedures in both sexes can alter vesical anatomy. Certainly in females with pelvic prolapse and/or stress incontinence, operations can successfully reposition the bladder and other pelvic organs towards normalcy. They also can cause difficulties if for example, bladder neck prolapse is overcorrected and obstruction occurs. Certain women will suffer urgency and frequency symptoms even if no obstruction is present.[9] In males, relief of obstruction at the level of the prostate may improve symptoms but changes in bladder configuration may not occur at the same rapid rate seen in symptom reduction. Furthermore, radical prostatectomy in the man with prostate cancer may alter bladder dynamics as well as cause sphincteric incontinence.[10] The anatomical changes of the ageing bladder are summarized in Table 104.1.

Bladder physiology and correlation to anatomy of the ageing bladder

Bladder function involves both the storage of urine and the expulsion of urine at a socially appropriate time. To maintain continence the storage of urine must occur under low pressures and the bladder must empty adequately. Unfortunately, ageing results in changes that occur intrinsically and extrinsically to the bladder that affect continence and emptying. Pathological changes are seen in the bladder due to ageing. In addition, nerve transmission can be altered due to age, disease states, surgical procedures, or drugs. Anatomic obstruction or lack of adequate support of the bladder neck also changes the ability of the bladder to empty and store urine.

The bladder consists of two parts: the body and the base or bladder neck. The smooth muscle fibres of the body are arranged randomly and those of the bladder neck are arranged in an inner longitudinal and outer circular layer. In the male urethra the sphincter consists of both smooth muscles and striated muscles. The external sphincter consists of the periurethral striated muscle and the intramural striated muscle or rhabdosphincter. In the female these muscle are attenuated. DeLancey proposes that female continence is created by a combination of muscular coaptation and passive compression of the urethra by the pubourethral hammock.[11]

Table 104.1 Anatomical changes of the ageing bladder.

Gross anatomical changes
Trabeculations
Cystocele (females)
Muscle loss at bladder neck (females)
Histological changes
Collagen deposition
Muscle degeneration
Axonal degeneration

During urine storage, low-level afferent bladder stimulation signals sympathetic contraction of the bladder neck and relaxation of the detrusor muscle or body of the bladder. This results in storage of urine under low pressure. The voiding reflex is initiated when afferent activity becomes intense. The pontine micturition centre stimulates the parasympathetic pathway and inhibits the sympathetic pathway resulting in relaxation of the bladder outlet and contraction of the detrusor muscle and thus bladder emptying. The striated external sphincter, which has separate innervation from the bladder neck, is also influenced by the pontine micturition and storage centres. The voiding reflex results in inhibition of the external sphincter and the storage reflex results in activation of the pudendal nerve.

The bladder must be able to distend and contract to adequately function. Structural changes in the tissues and abnormalities in bladder shape can alter urinary storage and emptying. Bladder compliance is a measurable value defined as the change in volume divided by the change in intravesical pressure. A normally functioning bladder fills under a low pressure therefore the bladder is compliant. Compliance is greatly affected by tissue composition, innervation and vascular supply.

Histological studies have shown that as collagen levels increase compliance is lost. Landau demonstrated that in bladders with poor compliance the ratio of type III to type I collagen was significantly higher than that of normal bladders.[12] The aged bladder has a higher deposition of collagen; in addition, innervation of the detrusor smooth muscle changes with age. Neurochemical studies of human detrusor strips have shown an increase in purinergic neurotransmission and a decrease in cholinergic neurotransmission with age. It is felt that the shift in neurochemical transmission may change the resting tone of the bladder and contribute to the overactive bladder symptoms in aged bladders.[13]

Bladder wall blood flow is affected by the intramural tension. A bladder with poor compliance has increased intravesical pressure and intramural tension therefore, a greater decrease in bladder blood flow. Ischaemia can result in diminished contractility and can result in patchy denervation. The end result is a bladder that poorly empties and may have detrusor instability.[14] Injured areas of the bladder can become weak and form diverticulum resulting in ineffective bladder emptying.

The complexity of voiding dysfunction in the aged bladder makes if difficult to determine changes in the bladder secondary to the normal ageing process versus changes as

the result of bladder outlet obstruction or diseases effecting the nervous system and/or vascular supply. Certainly the lower urinary tract symptoms of obstruction, instability and impaired detrusor function often overlap. The changes seen in bladder function with ageing must certainly overlap as well. A study by Homma found the symptoms of urgency, frequency and nocturia increased with age in both men and women. The cystometric capacity declined with age in both sexes.[15]

Histological changes in the aged bladder have been documented including increased collagen deposition, widened spaces between muscle fibres and ultrastructural changes of the smooth muscle cell membrane.[7] Elbadawi also showed that aged bladders without urodynamic evidence of obstruction had muscle cell membranes with dominant dense bands and depleted caveolae.[7] These finding were reproducible and different from the ultrastructural changes seen with obstruction, overactive or hypocontractile bladders. These findings are felt to represent dedifferentiation of the smooth muscle fibres.

Changes in bladder compliance, nerve transmission and vascularity occur as the bladder ages. Certainly multiple disease processes may worsen these changes. With advanced age expected bladder symptoms might include increasing frequency and urgency with a decreased bladder capacity.

Special disease states

Several disease states especially affect the bladder in the geriatric population. Whether caused by neurological disease, endocrine problems, iatrogenic intervention or the ageing process itself, these problems exact particular morbidity on the lower genitourinary tract. The following conditions are particularly important.

Parkinson's disease

Parkinson's disease affects 1% of all patients over the age of 60 and is rarely seen in those under 40. In addition to the characteristic tremors and motion deficits, the loss of dopaminergic neurons in the substantia nigra of the basal ganglia affects voiding by reducing the inhibitory effect of the basal ganglia on the micturition reflex as demonstrated in several animal studies.[16]

The voiding symptoms of Parkinson's disease are frequency, urgency and urge incontinence. These irritative symptoms are present in well over half of all patients with the disorder.[17] A significant problem from a diagnostic viewpoint is the presence of these symptoms in elderly males. These irritative voiding symptoms mimic the lower urinary tract symptoms (LUTS) associated with bladder outlet obstruction related to benign prostatic hyperplasia (BPH). Without urodynamic evaluation, the neurogenic component to the symptoms may be overlooked or not quantified well and inappropriate therapy instituted. Furthermore, men with multiple systems atrophy rather than in true Parkinson's disease may actually have mild detrusor-sphincter dyssynergia, which again could mimic the obstructive symptoms of BPH.[18]

The typical urodynamic findings of Parkinson's are detrusor hyperreflexia on filling cystometry. As much as 79% of bladder dysfunction in these patients can be related to hyperreflexia.[19] Other findings are not uncommon though. Hyporeflexia is present in 16% of patients in Araki's study.[19] Obstruction can also be present particularly in the male with prostatic enlargement or stricture disease from previous interventions. Multichannel urodynamics is essential to the evaluation of voiding dysfunction in patients with Parkinson's disease.

Cerebrovascular accident (CVA)

Stroke can be considered a major health problem among elderly patients. Approximately three-quarters of the roughly 400 000 stroke patients per year in the United States are over 65 years old. The impact of this disorder on voiding and continence can range from mild to profound. When occurring in the aged patient, its effects can magnify pre-existing bladder conditions and cause great confusion as to proper therapy. Depending on the location of the ischaemic event, the bladder may range from hyperreflexic to areflexic. One can therefore present with an entire range of symptoms anywhere from nocturia and urgency/urge incontinence to voiding difficulties and urinary retention.[20] The presence of urinary incontinence in the acute phase of a CVA is a powerful predictor of a negative outcome.[21]

The patient presenting with lower urinary tract symptoms following a CVA can be a diagnostic dilemma. In one study, detrusor hyperreflexia was seen in 68% of patients, detrusor-sphincter dyssynergia in 14%, and uninhibited sphincter relaxation in 36%.[20] In that same study, there were patients with retention who were noted to have detrusor areflexia with an unrelaxing sphincter. No correlation was seen between site of lesion and urodynamic findings. In the elderly post-CVA male, neurogenic bladder problems may coexist with obstruction from the prostate gland. Nitti found in a group of men with a mean age of 70 with voiding complaints following a stroke that detrusor hyperreflexia was present in 82% of the group, but pressure-flow characteristics of definite obstruction were present in 63%.[22] Multichannel urodynamics can be an important adjunct in the urological management of these patients.

Nocturia

Nocturia is commonly listed as a symptom by the older patients. In males it is often perceived as related to prostate

enlargement. But this symptom is commonly noted in ageing women.[23] Menopausal status may contribute to the presence of nocturia.[24] In all likelihood, nocturia is a manifestation of normal ageing.

Other factors impacting the presence of nocturia in the ageing individual include sleep difficulties and nocturnal polyuria. Sleep disturbances are common in the elderly population and nocturia may be more related to those problems as opposed to a urinary tract dysfunction. Furthermore, the patient with nocturia from whatever cause will have poorer sleep.[25] The problem of nocturnal polyuria in many of the elderly, which is reported as nocturia can be difficult to manage. With lower renal concentrating ability, poorer conservation of sodium, loss of the circadian rhythm of antidiuretic hormone secretion, decreased production of renin-angiotensin-aldosterone, and increased release of atrial natriuretic hormone, there is an age-related alteration in the circadian rhythm of water excretion leading to increased night-time urine production in the older population. Exacerbated by age-related diminution in functional bladder volume and detrusor instability, nocturnal polyuria often leads to a dramatic version of nocturia.[26] Whatever the cause, nocturia is a significant problem both from a QOL standpoint and as a risk factor for falls leading to hip fractures.[27] Essentially, nocturia more than twice per night is significantly associated with the risk of falls and subsequent fractures.

Dementias

The elderly patient with dementia faces the dual difficulties of having to face an ageing bladder with its consequences and in addition, the difficulties caused by an altered perception of his or her internal and external environments. This can lead to urinary incontinence and/or retention based on either bladder factors or due to central neurological misperceptions of urinary activity. The difficulties in management of these patients' other significant conditions often pushes concerns over incontinence aside but the fact is that incontinence issues are the primary cause for institutionalization of the elderly patient.

Evidence of combined cerebral and urinary tract dysfunction comes from perfusion studies in elderly patients. From PET scan studies it has been demonstrated that the pontine micturition centre in the dorsomedial pontine tegmentum, the periaqueductal grey matter and the pre-optic area of the hypothalamus are all active during various phases of micturition.[28] Furthermore, urge incontinence has been associated with underperfusion of the frontal areas of the brain.[29] Clearly, cerebral atrophy due to whatever cause can lead to disinhibition of the bladder and resulting incontinence. Treatment routines combining anticholinergic medications with prompted or timed voiding have been utilized to circumvent the loss of cerebral control over the micturition process in elderly patients afflicted with bladder dysfunction.[30]

Pharmacology as it relates to the ageing bladder

With so many elderly at risk for bladder dysfunction, the use of medications among the elderly for urinary tract problems is rising almost exponentially. The number of prescriptions for overactive bladder drugs number in the millions, many presumably to older sufferers of the condition. Clearly an understanding of how the common drugs for these urinary conditions work is essential to proper prescribing and monitoring. Proper use of pharmaceuticals for urinary conditions can give maximum benefit to the patient's symptoms and pathology without engendering any undue risk in the ageing population.

Receptors

The pharmacology of the bladder is primarily related to either the bladder itself or in the nervous innervation of the organ. At the level of the bladder itself, a number of receptor sites exist to varying degrees. These receptors govern to a great degree the function of the lower urinary tract and become more prominent in the elderly patient as various bladder conditions become more prevalent.

Among the adrenergic receptors, alpha and beta-receptors are found in the bladder although it has been thought that beta-receptors predominate in the bladder body and alpha-receptors in the bladder base and bladder neck region. Urine storage is facilitated by relaxation caused by beta stimulation and tonic contraction in the area enriched by alpha-receptors. More recent work has elucidated (at least in the rabbit) that the division by receptors into bladder base and body may be overly simplistic and that further regionalization of the bladder based on differing mixes of alpha- and beta-receptors might be more appropriate.[31] Alpha-receptors are also well characterized in the prostatic urethra and stroma. Stimulation of these receptors causes contraction and thus possibly obstruction of the bladder neck.[32]

Muscarinic receptors are the other major group of receptors influencing bladder behaviour. These receptors, particularly the M2 and M3 subtypes are responsible for bladder contraction.[33] The pharmacology of these receptors is influenced by their ubiquity. They are also found in gastrointestinal, airway and salivary gland smooth muscle. Table 104.2 gives a summary of receptors located within the bladder and the effects of ageing on these receptors.

Adrenergic stimulation/blockade

Alpha stimulation in the elderly patient is most often a deleterious side effect from a pharmaceutical designed for action elsewhere. With the rich supply of alpha-receptors

Table 104.2 Bladder receptors and ageing.

Receptor	Location	Action	Effect of ageing
Alpha- adrenergic	Prostate	Contraction	Stimulation – causes smooth muscle urinary retention Blockade – improves urine flow
Alpha- adrenergic	Bladder base	Contraction smooth muscle	Shift in subtype may ameliorate bladder symptoms
Beta-adrenergic	Bladder body	Relaxation smooth muscle	Unknown at present
Muscarinic	Detrusor muscle (primarily M3)	Relaxation smooth muscle	Urinary retention Worsening of side effects at other locations

in the prostate, stimulation can cause contraction and thus obstruction and urinary retention.[34] Alpha blockade, although originally designed with hypertension in mind, has become a mainstay in the therapy of lower urinary tract symptoms related to prostatic enlargement.[35]

One effect of ageing is the possible change in the type, sensitivity and number of these receptors. With increasing age, alpha adrenoceptor responsiveness either decreases or remains unchanged.[36] Furthermore, alpha-receptors in the ageing bladder itself show a shift from the alpha-1a subtype to an alpha-1d predominance.[37] If alpha-blockers have an effect in the bladder that aids in relief of lower urinary tract symptoms as well as its effect on obstruction itself, then this change with ageing could have implications for both short-term as well as long-term use in elderly men with prostate disease.

Antimuscarinics

These drugs are utilized primarily in the therapy of symptoms of overactive bladder. Although the M2 subtype is the predominant population, it appears the smaller population M3 subtype is the functionally important group.[38] Although several antimuscarinic agents exist in oral, intravesical and transdermal forms, the lack of bladder M3 selectivity remains a problem.

In the elderly, antimuscarinic can be very effective for symptoms of frequency, urgency and urge incontinence.[39] Changes in the ageing patient may, however, alter the pharmacology of these drugs in an adverse manner. Side effects such as dry mouth and constipation may be of more concern and less well tolerated in the elderly individual. Decreases in force of detrusor contraction in the ageing male with an enlarged obstructing prostate gland may well push the patient into urinary retention. At least one of these agents crosses the blood-brain barrier and thus particularly in the ageing patient could have a higher incidence of confusion as a side effect.[40] These effects could play a role in limiting the usefulness of the antimuscarinics in treating bladder dysfunction.

5-alpha reductase inhibitors

This group of drugs, although having therapeutic activity in the prostate gland, are known for their beneficial effect on the bladder complaints caused by obstruction from the prostate gland. These agents inhibit the conversion of testosterone to dihydrotestosterone in the prostate gland and thus cause reduction in the size of the periurethral prostatic tissue. This leads to improvement in urinary flow and BPH-related symptomatology. In the PLESS study, the main side effects in all age groups are sexual side effects particularly ejaculatory disturbances.[41] This may be more profound in the elderly male with borderline sexual dysfunction although this was not borne out in the PLESS study.

Surgical disease of the ageing bladder

Lower urinary tract surgery in the aged patient is common for two conditions with large impact on the bladder – stress urinary incontinence in women and bladder outlet obstruction from prostatic enlargement in men. The elderly suffer disproportionately from these disorders but have benefited from advances in therapy for these conditions. With proper selection of treatment, this group of patients can enjoy great improvement in their QOL related to their lower urinary tract. Furthermore, minimally invasive techniques for overactive bladder conditions have also evolved and may be useful in the older population.

Female stress urinary incontinence

Stress incontinence occurs when abdominal pressure generated by such actions as coughing, sneezing or other Valsalva manoeuvres causes bladder pressure to exceed urethral pressure without a detrusor contraction and urine is expelled. Stress incontinence is associated with parturition, previous pelvic surgery and ageing. Previously, major abdominal surgery was the only method considered for treatment and older age could be considered a relative contraindication. But with newer therapies, elderly women

can be considered excellent candidates for improvement in their condition.

Pelvic floor conditioning

Pelvic floor exercises have become a mainstay of conservative therapy for stress incontinence. They are absolutely safe and can be performed either alone or with biofeedback. Effectiveness as measured both subjectively by patient report as well as objectively with pad weights has been demonstrated in several studies.[42]

Some concern over the effectiveness in the elderly of pelvic floor rehabilitation can be raised. The reduction in estrogen effect on the vaginal tissues may reduce the benefit of these exercises in the elderly woman. Furthermore, the overall reduction of muscle tone with ageing may also make these exercises less efficacious.[43] Patients with significant intrinsic sphincter deficiency may not respond as well to pelvic floor conditioning. These exercises however are essentially risk-free which makes them especially appealing as a first-line effort in the elderly woman.

Pharmacological management

Stress urinary incontinence has been remarkably resistant to drug therapy in the past. Pharmacological agents with alpha-adrenergic properties such as pseudoephedrine were occasionally utilized with moderate success in women with mild incontinence.[44] These medications were effective due to the presence of alpha-receptors in the bladder neck. These agents though have more recently been pulled from use due to adverse events and so are not readily available for use. Estrogen therapy may also play a role in the medical management of stress incontinent in the older, postmenopausal woman[45] but its true benefit is controversial.

Anticholinergic agents, although truly indicated for urgency and urge incontinence, are often prescribed for stress incontinence. These drugs may be helpful in women with mixed incontinence (urge and stress incontinence) by reduction of the urge component and thus improving overall continence. In the patient with pure stress incontinence though, the patient may perceive a worsening of the problem in that the bladder capacity will increase and the patient will leak larger volumes of urine with stress manoeuvres.[46]

Although it is appealing to consider these pharmaceuticals as first-line therapy for stress incontinence in the ageing woman, one must consider certain factors. Alpha-adrenergic agents have been associated with cerebrovascular accidents and increases in blood pressure.[34] Certain anticholinergic medications cross the blood-brain barrier and can cause confusion and drowsiness in the older patient.[40] These adverse effects may outweigh the usually small benefits from these drugs on stress incontinence.

The serotonin-norepinephrine reuptake inhibitors (SNRIs) are being shown to have a therapeutic effect in female stress incontinence. These drugs have been shown to facilitate urine storage and facilitate rhabdosphincter activity. Thus a positive effect on stress incontinence could be expected and trials are underway to study this possibility.[47] Safety in the geriatric population would also need evaluation.

Injection therapy

The concept of injecting substances at the bladder neck to aid in coaptation and thus improve continence dates back to the use of sodium morrhuate by Murless in the 1930s.[48] This led later to the use of Teflon popularized by Politano with good results.[49] Concerns over the safety of Teflon injection led to the use of glutaraldehyde cross-linked bovine collagen and later development of other injectables such as carbon beads. Injection treatments have been shown to have an improvement rate of about 40%[50] with best results occurring in women without low leak point pressures or maximum urethral closure pressures.

This therapy may be a good alternative for the older female. It is minimally invasive with a low rate of complications. The anaesthetic requirements are not significant with some reporting use of local anaesthetic only. The major downside, especially for the geriatric patient is the frequent need for multiple injections to achieve success but newer injection materials may be longer lasting. Still, this is an excellent option for the older woman desiring aggressive treatment but reluctant to undergo major surgical procedures.[51]

Operative therapy

With multiple procedures described for female stress urinary incontinence, it is difficult to discern what the role of surgery might be for the ageing female. Several factors are clear though. Older women are, as a rule, healthier now and thus better able to tolerate surgery. Surgery offers the best chance for successful resolution of stress incontinence. Finally, modifications of many procedures have allowed good results with less morbidity than was seen with older operations.

Sling procedures have evolved from being a procedure designed only for those with severe incontinence to a rational alternative for all women desiring operative therapy.[52] The procedure is commonly done today with alternative materials for the sling such as cadaveric fascia or dermis as opposed to the classic descriptions of harvesting the patient's own fascia. Fixation can be accomplished either at the rectus fascia or at the pubic bone.

The taping procedures for stress incontinence have also shown good results with minimal morbidity and may be ideal alternatives for the elderly female. The tension-free vaginal tape procedure as popularized by Ulmsten[53] and its modifications (suprapubic tapes and transobturator tapes) place a sling-like material at the midurethra and are often done under local anaesthetic with light sedation only.

These procedures have been shown to be safe enough and have good enough results to be a reasonable alternative for the more active older female who requires aggressive treatment but desires minimal morbidity.[54] Newer fixation approaches lend themselves well to a transvaginal approach.

Benign prostatic hyperplasia (BPH) in the older male

Benign enlargement of the prostate gland in the human male is a condition inexorably linked with ageing. When the vesicourethral junction becomes obstructed by the growing tissue, symptoms such as slowing of the urinary stream, hesitancy, straining to void and a sensation of incomplete emptying result. Furthermore, irritative symptoms such as urinary frequency, urgency and nocturia may also become common. It is estimated that the prevalence of symptoms related to BPH may be as high as 50% in a multinational survey.[55]

Medical therapy

Two broad classes of drugs are utilized as therapy for BPH, alpha-receptor blockers and 5-alpha reductase inhibitors. The bladder neck region in males is rich in alpha-receptors and blockade of these causes relaxation of the smooth muscle in the prostatic urethra. This results in a decrease in the tonic luminal pressure in the prostatic fossa and allows for more efficient urine outflow from the bladder.[56]

Early alpha-antagonists were designed primarily for use as antihypertensives and thus a major side effect when used for relief of voiding dysfunction from BPH was orthostasis. Normotensive men complained also of asthenia and fatigue.[57] In older men with hypertension, attempted medical management of BPH along with hypertension became complex. Over the last several years, the introduction of alpha-adrenergic antagonists selective to the prostatic alpha-receptors has broadened the population that can be managed with these agents and includes with safety many elderly men.[35]

The 5-alpha reductase inhibitors block the conversion in the prostate gland of testosterone to dihydrotestosterone, which is the active form stimulating prostate growth. With blockade, the prostate gland involutes and a reduction in prostate volume of up to 30% may be seen. This can result in an improvement in urinary flow and a decrease in symptomatology. The safety profile of these drugs is very good making them a good choice in the older male particularly those with very large prostate glands.[41]

Combination therapy may also be of benefit in the elderly male. The recently completed Medical Therapy of Prostate Symptoms (MTOPS) study demonstrated a 66% decrease in acute urinary retention compared to placebo. Alpha blockade alone and 5 alpha-reductase therapy alone showed 39% and 34% reductions respectively.[58] Acute urinary retention in the elderly is a morbid event with an impact on QOL similar to that of myocardial infarction so prevention via combined therapy may be worthwhile for the older population with lower urinary tract symptoms related to BPH.

Minimally invasive therapy

A plethora of minimally invasive treatments for BPH now exist. Many are safe enough to be office based and thus particularly applicable to the older male population. These therapies involve the delivery of energy to the prostate gland in order to heat the tissues to greater than 60° C which leads to protein denaturation and ultimately destruction of prostatic tissue and relief of obstruction. The differences in the methods lie in the delivery system whether by externally generated microwaves[59] or internally placed systems for radiofrequency energy[60] or laser energy.[61]

Safety makes these procedures particularly appealing for the older male.[62] Most of the complications centre around irritative voiding symptoms. Bleeding essentially does not occur but post-procedure retention can be a problem. Furthermore, it takes several weeks before improvement in symptoms and flow occurs.

Transurethral resection of the prostate gland (TURP)

This procedure is still considered the 'gold standard' of treatment for bladder outlet obstruction from BPH.[63] It works quickly since the obstructing tissue is removed immediately at the time of surgery. Symptom scores drop rapidly and flow rates are instantly improved. Although not without morbidity, improvements in instrumentation and optics have made this procedure much safer for the elderly patient and in those with severe symptoms or retention it is still the best choice for therapy no matter the age of the patient if he can reasonably tolerate anaesthesia.

Minimally invasive therapy of overactive bladder

Since many older patients do not tolerate anticholinergic/antimuscarinic drugs well, alternatives for urgency/frequency type symptoms have been sought. The techniques involve modification of the neural pathways leading to muscular contraction in the bladder. Submucosal injection of botulinum toxin under cystoscopic guidance leads to chemodenervation at the motor terminal and increases in bladder capacity and decreases in detrusor pressure.[64]. Sacral nerve stimulation also is an effective mode of treatment for symptoms of urgency and frequency. With this technique, a programmable generator sends electrical impulses along the S3 nerve root thus stimulating the innervation of the pelvic floor. Aboseif demonstrated a large reduction in costs associated with bladder complaints after implantation of this stimulator.[65]

Conclusion

The effects of ageing on lower urinary tract function and dysfunction can be profound. Anatomic variations, both at the macroscopic and ultrastructural levels occur frequently and induce functional changes. Disease states commonly seen in the older patient have significant impact on the bladder, which should be recognized as a major portion of the syndromes. Bladder changes from ageing significantly impact on pharmaceutical effectiveness and alter the ability to manage many conditions. A multimodal approach including surgery to common geriatric disorders of the lower urinary tract can be safe and very effective.

Key points

- Bladder anatomy changes with ageing both macroscopically due to prostate enlargement in men and pelvic prolapse in women as well as microscopically due to collagen deposition.
- Changes in anatomy lead to physiological changes such as loss of compliance and variation in response to neurotransmitters and pharmaceuticals
- Certain extravesical disease processes common in the older patient have a profound effect on the bladder.
- The common lower urinary tract symptom complexes of stress incontinence in women and obstructive voiding in women can be safely treated by a variety of means including surgery.

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CHAPTER 105

Prostate diseases

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Introduction

The prostate is a small gland, surrounding the urethra, located between the penis and the bladder. The prostate is perhaps the most disease-affected organ in the male body. The three main conditions that can affect the prostate are:

- Benign prostatic hyperplasia (BPH), that is, an enlarged prostate that causes urinary problems. It is a common condition that is associated with ageing. About 60% of men who are 60 years of age or over have some degree of prostate enlargement. BPH can be treated with medication, a minimally invasive procedure or, in extreme cases, surgery that removes the prostate.
- Cancer of the prostate is one of most common cancers in men over 65 years old. The risk of developing prostate cancer increases with age. The progression of this cancer is very slow and it can take up to 15 years to develop metastasis (most often in bones), so the specific mortality is weak. The screening of prostate cancer is based on digital rectal examination and prostate-specific antigen (PSA) assay. Prostate cancer can be cured when treated in its early stages. Treatments include removing the prostate, hormone therapy and radiotherapy. All the treatment options carry the risk of significant side effects, including loss libido, sexual dysfunction and urinary incontinence.
- Prostatitis is inflammation of the prostate gland. There are different forms of prostatitis based on causes and chronology (acute or chronic). The inflammation can be due to bacterial infection with an acute or chronic presentation. These forms are treated with antibiotics. Most often (in ~95% of cases) the diagnosis is a chronic non-bacterial prostatitis or male chronic pelvic pain syndrome that is treated with a large variety of modalities.

This chapter reviews these main diagnostic entities and the approach to treatment in the ageing male.

Benign prostatic hyperplasia

BPH is very common and its incidence is correlated with the ageing population. Autopsy data show that nearly 90% of all men aged 80 years and above have anatomical or microscopic evidence of hyperplasia and that pathology is found in half of men in their 50s.[1]

BPH is commonly associated with bothersome lower urinary tract symptoms (LUTS) such as urinary frequency, urgency, nocturia, decreased and intermittent strength of stream and the sensation of incomplete bladder emptying, which can seriously impair quality of life.

The term 'BPH' actually refers to a histological condition, namely the presence of stromal-glandular hyperplasia within the prostate gland.[2] The condition becomes clinically relevant if and when it is associated with bothersome LUTS. However, the relationship between BPH and LUTS is complex, because some men with histological BPH will develop significant LUTS, whereas other men who do not have histological BPH will develop LUTS.[3] Epidemiology, clinical expressions, diagnostic approach and treatment of BPH are discussed is this chapter.

Epidemiology

Mortality

BPH is a common problem among elderly men and leads to substantial disability. However, it is not a frequent cause of death. Mortality from BPH declined dramatically in industrialized countries from the 1950s to the 1990s.[4] Moreover, a cohort study of 4708 men who underwent transurethral resection of the prostate (TURP) between 1976 and 1984 at the Kaiser Permanente Medical Center in Oakland, OR, revealed no greater mortality than age-matched men who did not undergo TURP.[5]

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

The decrease in mortality can result either from a reduction in disease prevalence or from improvements in survival. To date, there is no evidence that the decrease in BPH mortality is likely to be related to improvements in medical and surgical treatments provided. Indeed, it could be considered as a health care performance indicator.[6]

Prevalence

BPH is increasingly common with advancing age. About 8% of men aged 31–40 years show histological evidence of BPH. This rate increases sharply to 50, 70 and 90 in men aged 51–60, 61–70 and 81–90 years, respectively.[7] Clinical BPH, defined by moderate-to-severe LUTS, occurs in ~25% of men aged 50–59 years, in 33% of men aged 60–69 years and in 50% of men older than 80 years.[7] Aetiologies of LUTS are multifactorial but BPH is a major contributing factor. Age-elated, detrusor dysfunction, neurogenic disease and diabetes are other major causes of LUTS.[8] The prevalence of LUTS in Europe varies with age, ranging from 14% in the fourth decade to >40% in the sixth decade. Based on an overall prevalence of LUTS of 30%, approximately four million men older than 40 years suffer from LUTS in the UK.[9] Furthermore, with the ageing population, the prevalence of BPH and its impact on medical practice will increase dramatically in the future.[3]

Pathogenesis and risk factors of BPH

BPH initially grows in the periurethral or transitional zone, with a fourfold increase in stromal tissue and a twofold increase in glandular components. However, the pathogenesis of BPH remains vague. Multiple factors contribute to the development of BPH[10] but the two main ones are changes in hormone level with age. Thus, the development of BPH requires both functional Leydig cells and ageing. However, given that testosterone, dihydrotestosterone and estrogen may be involved in BPH development, these hormones are not sufficient to cause BPH. Other factors influence the risk of developing BPH:

- *Age:* Several studies have demonstrated a relationship between age and markers of BPH progression.[11,12]
- *Genetic susceptibility:* Positive family history of BPH increases the risk of having more moderate to severe LUTS.[13] Moreover, twin studies suggest that heredity is a more important determinant of lower urinary tract symptoms than age, transition zone volume or total prostate volume.[14]
- *Race:* Black men are more likely than white men to have more moderate to severe LUTS.[13] In contrast, Asian men are less likely than white and black men to have BPH.[15]
- *Free PSA levels:* Higher free PSA levels increase the risk of BPH.[16]
- *Heart disease:* Heart disease increases the risk of BPH.[16]
- *Physical activity:* Lack of physical exercise increase the risk of BPH.[16]
- *Inflammation:* Epidemiological data show a strong relationship between prostatitis and BPH.[17]
- *Medications:* Use of β-blockers increases the risk of BPH.[16]
- *Other factors:* Conditions such as hyperinsulinaemia, dyslipidaemia, elevated blood pressure and obesity have been identified as risk factors of BPH.[18,19]

Natural history

Lower urinary tract symptoms (LUTS) include increased frequency of urination, nocturia, hesitancy, urgency and weak urinary stream. These symptoms typically appear slowly and progress gradually over years. Untreated BPH can cause acute urinary retention (AUR), recurrent urinary tract infections, hydronephrosis and renal failure.

One of the largest longitudinal studies, the Olmsted County study conducted in the USA, enrolled 2215 men aged 40–79 years. At 92 months' follow-up, 31% of participants reported a ≥3-point increase in AUA Symptom Index (AUA-SI; identical with the seven symptom questions of the IPSS) score and the mean annual increase in AUA-SI was 0.34 points.[20,21] Moreover, in the placebo arm of the Medical Therapy Of Prostatic Symptom (MTOPS) study, the overall clinical progression rate (defined as an increase in AUA-SI of ≥4 points, AUR, urinary incontinence, renal insufficiency or recurrent urinary tract infections) was 17.4% over the 4 year follow-up. About 78% of progression events were worsening symptoms.[22]

Although AUR and surgery are less common than overall symptomatic worsening, they represent important progression events with financial, emotional and health-related consequences for patients. Untreated men with symptomatic BPH have about a 2.5% per year risk of developing AUR.[23,24] Age, LUTS, urinary flow rate and prostate volume are risk factors for AUR in population-based studies, but not in all clinical trials. Moreover, serum PSA seems to be a stronger predictor of prostate growth than age or baseline prostate volume[25] and should be a good risk predictor of AUR.[22]

Diagnostics

Patient evaluation

Urinary symptoms may be evaluated using the American Urologic Association (AUA) symptoms score or the International Prostate Symptoms Score (IPSS) (Table 105.1).

The AUA symptom score should only be used to assess the BPH severity symptoms (not for differential diagnosis). It includes seven questions: frequency, nocturia, urinary stream weakness, straining, intermittency, incomplete emptying and urgency. Each of these items is scored on a scale from 0 (not present) to 5 (almost always present). Symptoms

Table 105.1 AUA Benign Prostatic Hyperplasia Symptom Score (AUA Practice Guidelines Committee, 2003).

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
Over the last month how, often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
During the last month, how often have you had to urinate again less than 2 h after you finished urinating?	0	1	2	3	4	5
During the last month, how often have you stopped and started again several times when you urinate?	0	1	2	3	4	5
During the last month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
During the last month, how often have you had a weak urinary stream?	0	1	2	3	4	5
During the last month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
During the last month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	None	1 time	2 times	3 times	4 times	5 or more times

Add the score for each number above and write the total in the space to the right
SYMPTOM SCORE = 1–7 MILD; 8–19 MODERATE; 20–35 SEVERE. TOTAL_____

are classified from mild (total score 0–7) to moderate (total score 8–19) or severe (total score 20–35). The AUA symptom score is a useful tool for assessing symptoms over time in a quantitative way. The International Prostate Symptom Score (IPSS) uses the same items and adds a disease-specific quality of life question: 'If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?'.

However, before one concludes that a man's symptoms are related to BPH, other disorders which can cause similar symptoms should be excluded by history, physical examination and several simple tests.

The history may provide important diagnostic information:

- History of type 2 diabetes: nocturia.
- Symptoms of neurological disease: neurogenic bladder.
- Sexual dysfunction related LUTS.
- Gross haematuria or pain in the bladder area: bladder tumour or calculi.
- History of urethral trauma, urethritis or urethral instrumentation: urethral stricture.
- Family history of BPH and prostate cancer.
- Treatment with drugs that can impair bladder function (anticholinergic drugs) or increase outflow resistance (sympathomimetic drugs).

Physical examination should include digital rectal examination (DRE) to assess prostate size and consistency and to detect nodules or induration suggesting a prostate cancer. Rectal sphincter tone should be determined and a neurological examination performed.

A general health and cognitive status evaluation is useful for choosing the best treatment, especially if a surgical procedure is required. Clearly, dementia among many neurological conditions could affect urinary condition.

Laboratory evaluation

Urinalysis should be done to detect urinary infection and haematuria. Urine cytology may be helpful for bladder tumour diagnosis in men with predominantly irritative symptoms (frequency, urgency, nocturia) or haematuria especially with a smoking history.

A high serum creatinine may be due to bladder outlet obstruction or to underlying renal or prerenal disease; it also increases the risk of complications and mortality after prostatic surgery. Serum creatinine used to be recommended, but studies have shown that it is not mandatory without comorbidity.[26] In contrast, the European Association of Urology considers it to be a cost-effective test. Bladder, ureters and kidneys ultrasounds are indicated if the serum creatinine concentration is subnormal.

PSA measurement remains controversial. Serum PSA specificity in men with obstructive symptoms is lower compared with asymptomatic patients. PSA is not cancer specific and could be increased in different prostatic

disorders, including BPH. Moreover, 25% of patients with a prostate cancer have a normal PSA (4.0 ng ml^{-1} or less, a widely used cut-off value).

Regarding BPH guidelines,[26] recommendations refer to patients with a life expectancy of >10 years.

Treatment[2]

LUTS of BPH progress slowly, with some patients progressing more rapidly than others. The physician can predict the risk of progression from the patient's clinical profile. Also, increased symptom severity, a poor maximum urinary flow rate and a high post-void residual urine volume are major risk factors for overall clinical progression of LUTS/BPH.[27] Also, therapeutic decision-making should be guided by the severity of the symptoms, the degree of bother, the patient's risk profile for progression and patient preference. Information on the risks and benefits of BPH treatment options should be explained to all patients.

The treatment for LUTS can be separated into four groups: watchful waiting, medical therapy, minimally invasive treatment and invasive surgical therapy.

Watchful waiting

Patients with mild symptoms (IPSS <7) should be counselled about a combination of lifestyle and watchful waiting. They should have periodic physician-monitored visits. Patients with mild symptoms and severe bother should undergo further assessment.

A variety of life style changes may be suggested:

- fluid restriction, particularly prior to bedtime
- avoidance of caffeinated beverages and spicy foods
- avoidance/monitoring of some drugs (e.g. diuretics)
- timed or organized voiding (bladder retraining)
- pelvic floor exercises
- avoidance or treatment of constipation.

Medical treatment

α-Blockers

α-Blockers are an excellent first-line therapeutic option for men with symptomatic bother who desire treatment. Alfuzosin, doxazosin, tamsulosin, terazosin and silodosin are appropriated treatment options for LUTS secondary to BPH. They do not alter the natural progression of the disease. Adverse side effects commonly reported with different alpha-blockers include dizziness, headache, asthenia, postural hypotension, rhinitis and sexual dysfunction, most commonly occurring in ~5–9% of patient populations.

5α-Reductase inhibitors

The 5α-reductase inhibitors (duasteride and finasteride) are appropriate and effective treatments for patients with LUTS associated with demonstrable prostatic enlargement. Because of the mechanism of action, it takes 3–6 months for full clinical effect.

Combination therapy

The combination of an α-adrenergic receptor blocker and a 5α-reductase inhibitor is an appropriate and effective treatment strategy for patients with LUTS associated with prostatic enlargement. The MOST trial demonstrated maximum effect in reducing prostate size and improving symptoms by combining an α-blocker (doxazosin) with an α-reductase inhibitor (finasteride).[22] Combination medical therapy can effectively delay symptomatic disease progression, while combination therapy and/or 5α-reductase monotherapy is associated with decreased risk of urinary retention and/or prostate surgery. Patients successfully treated with combination therapy may be given the option of discontinuing the α-blocker after 6–9 months of therapy. If symptoms recur, the α-blocker should be restarted.

Role of anticholinergic medications

Evidence suggests that for selected patients with bladder outlet obstruction due to BPH and concomitant detrusor overactivity, combination therapy with an α-receptor antagonist and anticholinergic can be helpful.[28]

Caution is recommended, however, when considering these agents in men with an elevated residual urine volume or a history of spontaneous urinary retention. These kinds of medications also increase the risk of delirium in patients with cognitive impairment.

Phytotherapies

Phytotherapies for BPH are becoming increasingly popular and, although many physicians remain sceptical of their value, patients generally seem satisfied with their utility. Two of the more common herbal medications used include *Serenoa repens* (saw palmetto) and *Pygeum africanum* (*Prunus africana*). They have shown some efficacy in several small clinical series but cannot be recommended as the standard treatment of BPH.

Minimally invasive treatment

Transurethral microwave therapy (TUMT)

TUMT is a reasonable treatment consideration for the patient who has moderate symptoms, small to moderate gland size and a desire to avoid more invasive therapy for potentially less effective results.[29] TUMT may be associated with a higher retreatment rate over a 5 year follow-up interval than for men receiving TURP.[29]

Transurethral needle ablation (TUNA)

TUNA is an other minimally invasive therapy recommended as treatment options. The TUNA device is a rigid cystoscope-like instrument passed transurethrally under vision. Utilizing a radiofrequency signal, the tissue is

heated to between 46 and 100 °C. TUNA may be a therapeutic option for the relief of symptoms in the younger, active individual in whom sexual function remains an important quality of life issue (less risk of retrograde ejaculation); however, limited data are available on long-term outcomes.[30]

Surgery

Transurethral resection of the prostate (TURP)

A TURP can be performed with a regional block under or general anaesthesia. The procedure takes 60–90 min and generally requires a 24 h observation period in the hospital. A resectoscope loaded with a diathermy loop is introduced into the bladder. Under direct vision, strips of prostatic adenoma are resected one at a time and dropped into the bladder. This is continued until the entire adenoma is resected. At the end of the operation, the prostate chips are evacuated from the bladder and haemostasis achieved with electrocautery. The prostatic fossa is left with a wide open, bound by its capsule. The cavity will be lined by a regenerated epithelial surface in 6–12 weeks. Until the fossa is completely epithelialized, the patient is vulnerable to bleeding; the patient should avoid straining for at least 6 weeks.

TURP remains the gold standard treatment for patients with bothersome moderate or severe LUTS who request active treatment or who either fail or do not want medical therapy. Furthermore, patients should be informed that the procedure may be associated with short- and long term complications.[31] For frail patients, transurethral plasma vaporization of the prostate in saline (TUVis) could be useful. As opposed to the conventional transurethral resection of the prostate, this new procedure does not cut and shave off tissue with a loop but energetically vaporizes the tissue with a small electrode. Bleeds during and after this surgery can be avoided. This surgical technique should be proposed to frail patients especially with blood thinner treatments.

Transurethral incision of the prostate (TUIP)

TUIP is appropriate surgical therapy for men with prostate gland sizes <30 g. These patients should experience symptom improvements similar to TURP with a lower incidence of retrograde ejaculation.[32]

Laser prostatectomy

Several methods for laser prostatectomy have been developed, including ultrasound- and endoscopic-guided approaches.[33] A systematic review evaluated 20 randomized trials involving 1898 patients, including 18 comparing TURP with contact lasers, non-contact lasers and hybrid techniques:[34]

- The pooled percentage improvements for mean urinary symptoms ranged from 59 to 68% with laser treatments and from 63 to 77% with TURP.
- Improvements in mean peak urinary flow ranged from 56 to 119% with laser treatments and from 96 to 127% with TURP.
- Laser-treated subjects were less likely to require transfusions (<1 versus 7%) or develop strictures (4 versus 8%) and their hospitalizations were 1–2 days shorter.
- Surgical reintervention occurred more often after laser procedures than TURP (5 versus 1%).

Data were too limited to draw conclusions about the preferred laser technique or to compare laser treatment with other minimally invasive procedures, but patients treated with non-contact laser prostatectomy were more likely to have dysuria than patients treated with TURP or contact laser prostatectomy. In many centres, laser treatment of BPH has evolved from coagulation to enucleation with the holmium laser (HoLEP: holmium laser enucleation of the prostate). This instrument is not dependent upon prostate size and tissue can be preserved for histology. A meta-analysis of four small randomized trials comparing TURP with HoLEP found significant heterogeneity across studies, but concluded that peak flow rates were similar after either therapy and that TURP required less operating room time but resulted in more blood loss, longer catheterization times and longer hospital stays.[35]

Open prostatectomy

Open prostatectomy accounts for <5% of operations for BPH in the USA,[36] but it is performed more often in other countries. Open prostatectomy remains indicated for men whose prostates, in the view of the treating urologist, are too large for TURP for fear of incomplete resection, significant bleeding or the risk of dilutional hyponatraemia.

Prostate cancer

Epidemiology

Prostate cancer is an extremely frequent malignant disease. It represents the second most common cancer in men after lung cancer and the fifth cause of death by cancer in the world. According to GLOBOCAN statistics, 6 79 023 new cases of prostate cancer were diagnosed worldwide in 2002 and 2 21 002 men died of this disease during the same year, representing 5.8% of cancer mortality in humans.[37]

The epidemiological impact of prostate cancer varies from one country to another because of health policies or screening, but Western countries such as the USA, Australia and New Zealand and Western Europe are particularly concerned. Given the ageing population and its increasing incidence with age, prostate cancer affects mainly elderly men. In the USA, according to SEER data (Surveillance Epidemiology and End Results) from 2000 to 2005, the median age at diagnosis of prostate cancer was 68 years, with 25.7% of cases diagnosed in men ≥75 years of age.

Over 90% of deaths occurred in men ≥65 years of age and 71.2% in men ≥75 years of age.[38]

Principal individual risks factors of developing a prostate cancer are increasing age and heredity and ethnicity. In the USA, compared with white men, black men have a 40% higher risk of the disease and twice the rate of death.[39] Exogenous factors (food consumption, pattern of sexual behaviour, alcohol consumption and occupational exposure) may have an important impact on this risk. Several ongoing large randomized trials are trying to clarify the role of such risk factors and the potential for successful prostate cancer prevention.[40]

Diagnosis and screening

In the PSA era, procedures for prostate cancer diagnosis have changed considerably. Diagnosis is based clinically, on digital rectal examination (DRE), and biologically, on PSA assay. Diagnosis is confirmed by pathological evaluation of prostate biopsies. Regarding pathology, adenocarcinoma represents 98% of cases and most often arises from the peripheral part of the prostate. Among pathological features, differentiation of tumour tissue given by the Gleason score is particularly important.[39,40]

Based on the preliminary results of large ongoing screening trials, widespread mass screening is not appropriate at present. However, major urological societies recommend early diagnosis in well-informed men.[40] Thus, the French Urological Association (AFU) recommends performing a DRE and PSA test per year from age 55 years (or 45 years if there are risk factors) to 69 years according to the results the results of the European screening study ERSPC. Before 55 and after 69 years, tests should be proposed based on individual criteria.[41]

For elderly patients, in case of symptoms, it is necessary to obtain pathological evidence of prostate cancer to propose specific management. Therapeutic options (hormonal therapy, radiotherapy, analgesics) are usually feasible in this situation.

For asymptomatic patients, it is necessary take into account the individual probability of survival to propose early diagnosis tests. It is important, however, to maintain regular DRE assessment in older men to detect the onset of locally advanced prostate cancer potentially responsible for disabling symptoms. In this situation, even frail elderly patients may benefit from the specific treatment.

Management of localized prostate cancer

The management of localized prostate cancer[40] is based on classifications depending on relapse risk. The most widely used classification is that of D'Amico *et al*.[42] Patients are divided into three groups depending on the probability of biological relapse after local treatment of prostate cancer by surgery, radiotherapy or brachytherapy. This classification is based on DRE, PSA and Gleason score (Table 105.2).

Low-risk patients

- Watchful waiting:

Eligibility criteria

  - DRE T1 or T2a (Table 105.3)
  - PSA <10 ng ml^{-1}
  - Gleason score ≤6, no grade 4
  - ≤2 positive biopsies
  - ≤50% of cancer in each biopsy.

- Radical prostatectomy (bilateral ilio-obturator lymphadenectomy is optional).
- Brachytherapy:

Eligibility criteria

  - ≤cT2b
  - PSA <10 ng ml^{-1}
  - Gleason score ≤6
  - prostatic volume ≤50 cm^3
  - IPSS <12.

- Conformational external beam radiation therapy (prostate volume alone, dose of 70 Gy or more).

Intermediate-risk patients

- Radical prostatectomy with lymphadenectomy.
- Conformational external beam radiation therapy dose ≥74 Gy.
- Conformational external beam radiation therapy with a short course of hormonal therapy with LH–RH agonists (6 months).

High-risk patients

- The standard of care is the association of conformational external beam radiation therapy with hormonal therapy (if life expectancy exceeds 10 years).

Table 105.2 Groups of D'Amico *et al*.[42]

Low risk	Intermediate risk	High risk
Stage <T2b *AND* PSA ≤10 ng ml^{-1} *AND* biopsy Gleason score <7	Stage T2b *OR* 11≤ PSA ≤20 ng ml^{-1} *OR* biopsy Gleason score = 7	Stage ≥T2c *OR* PSA >20 ng ml^{-1} *OR* biopsy Gleason score ≥8

Table 105.3 TNM classification.

T1–T2	*Localized prostate cancer not extending beyond the capsule (no lymph node, absence of metastasis, that is, N0M0)*
T1	*Only histological finding (not visible to imaging and non-palpable)*
T1a	<5% of cancer cells on the samples
T1b	>5%
T2	*Cancer palpable on rectal examination*
T2a	Cancers with <50% of both prostate lobes
T2b	>50%
T2c	Involvement of both lobes
T3: Extension of cancer in the peripheral tissues (crossing of the prostate capsule)	
T3a	Extension beyond capsule
T3b	Involvement of seminal vesicles
T4: extension to adjacent organs: bladder, rectum, pelvic wall	
N0 or N1	Absence or presence of lymph node(s)
M0 or M1	Presence or absence of metastasis(es)

- A long-term adjuvant hormonal therapy (3 years) is beneficial.
- The radiation dose must be at least 70 Gy.
- Irradiation of pelvic lymph nodes is optional; it will be performed according to the risk of lymph node invasion.
- Non-conservative radical prostatectomy with lymphadenectomy is an option for locally advanced tumours with low metastatic risk in patients with long life expectancy and as part of a multimodal treatment.

Treatment modalities for localized prostate cancer in the elderly

Total prostatectomy

Technically, this is associated with bilateral resection of seminal vesicles and may be associated with bilateral pelvic lymph node dissection according to the prognostic group of D'Amico *et al*.[42] Radical retropubic prostatectomy or perineal prostatectomy is performed through open incisions. More recently, laparoscopic and robot-assisted prostatectomy have been developed. Available data are not sufficient to show differences in terms of oncological and functional results between these different techniques.[40]

Although data are limited, no significant differences exist between oncological outcomes and morbidity and mortality of radical prostatectomy done in the elderly compared with younger patients, apart from erectile dysfunction and urinary continence, which is more frequent in men ≥75 years of age. However, patient selection appears to be an important element in ensuring a balance between the expected benefit of surgery and the risks involved. This selection appears clearly from series available in the literature and corresponds perfectly with the 'oncogeriatric approach'.[40,43–47]

Radiotherapy

Technically, the current standard is 3D conformational radiotherapy, which can be further optimized by intensity modulation technology (IMRT).

These technological advances actually allow dose escalation in the volume to be treated to improve local control without increasing acute side effects on critical organs, particularly the bladder and rectum. Available data on the late side effects also appear to be in favour of IMRT.

In the literature, efficacy and tolerability of radiotherapy are not dependent on age. Nevertheless, comorbidities should be taken into account because they have an impact on the incidence of complications, particularly diabetes and vascular disease. Tolerance also depends on the size of irradiation fields. Irradiation of pelvic lymph node will be avoided if the probability of pelvic lymph node involvement is low.

Similarly, the possibility of associating a hormone therapy for 6 months in the intermediate prognosis group, which is a standard for younger patients, should be assessed with caution in elderly patients with moderate to severe comorbidities. The side effects of hormonal treatment could reduce or cancel the benefit in terms of overall survival. On the other hand, it appears that the benefit of hormone therapy in combination with radiotherapy in high-risk forms is found in elderly patients without or with minor comorbidities.[38,40,43,48–52]

Brachytherapy

Brachytherapy is a curative treatment of prostate cancer, most often consisting in the introduction of permanent implants of iodine-125 in the prostate gland. The implantation is performed by the perineal route under ultrasound guidance during general anaesthesia or spinal block.

This technique is used to deliver a very important dose in prostate volume, while sparing relatively periprostatic tissues, the dose falling rapidly at the periphery of the settlement area. Brachytherapy is therefore indicated in tumours with good prognosis: usually Gleason ≤6, initial PSA ≤10 $ng\,ml^{-1}$, absence of capsular damage and low proportion of adenocarcinoma on core biopsies.

This technique should not be applied in case of severe pre-existing urinary dysfunctions, in patients with a history of transurethral resection of prostate or in case of too large a prostate volume (>55 cm^3).

In terms of tolerance, the most frequent complications of brachytherapy arise in the urinary tract or rectum or affect erectile function. They are related to age and comorbidities which are a stronger predictor than age in multivariate analysis.[38,40,43,53]

Active monitoring

Currently, because of the widespread early diagnosis of prostate cancer through PSA testing, more and more

prostate cancers are found with size and aggressiveness presumed to be low. Many men with localized prostate cancer will not, in fact, benefit from a definitive treatment. In order to reduce the risk of over-treatment in these patients, conservative management strategies have been proposed.

For elderly patients, a waiting strategy may be proposed in several situations:

- Good prognosis disease according to the classification of D'Amico *et al*.,[42] since in this group, the specific risk of death is almost zero in patients over 70 years old.
- Low individual probability of survival due to a very advanced age or severe comorbidities.
- Patients who wish to avoid or delay the side effects of curative treatments.

The advantages of such a strategy are obvious, since it allows the patient to avoid treatment and side effects. However, it often induces anxiety in the patient and his family. It can also lead to a delayed diagnosis with a risk of more advanced disease.[38,40,43]

High-intensity focused ultrasound (HIFU)

This technique is still under evaluation. The high-intensity focused ultrasound is administered through the rectum, under general or spinal anaesthesia and guided by echography. Transurethral resection of the prostate to prevent postoperative urinary retention is mandatory. When validated, this technique will be useful in patients with small to moderate prostate volume and in patients relapsing after radiotherapy.

Other techniques such as cryotherapy and focal treatments are currently being developed, and will certainly soon strengthen our therapeutic tools.[38,40,43,54,55]

Hormone therapy

Hormone therapy alone is a treatment modality widely used in elderly patients with localized prostate cancer but considered unable to receive curative treatment. Nevertheless, these treatments are associated with a significant number of side effects, with an important impact on quality of life in elderly patients. Moreover, recent studies have shown a clear advantage for combined radiotherapy and hormone therapy in terms of progression-free survival and even overall survival in comparison with hormone therapy alone.

Hormone therapy alone should be considered only in symptomatic patients whose life expectancy is short due to significant competitive comorbidities.[38,40,43,54,56–61]

The management of localized prostate cancer in an elderly man is possible, but is it beneficial for the patient? To answer this question, some authors have tried to model the value of a curative treatment of prostate cancer in elderly men using a Markov model. Alibhai *et al*.[62] compared the probability of survival adjusted for quality of life (QALE) of patients stratified on age and differentiation of prostate cancer, according to their management by active surveillance, surgery or radiotherapy. They concluded that there was no advantage to treat patients >70 years of age with well-differentiated prostate cancer whatever their level of comorbidity. On the other hand, a benefit in terms of survival and QALE was found in patients >70 years of age with moderately to poorly differentiated prostate cancer including patients with intermediate comorbidities.

Advanced and metastatic prostate cancer

Despite earlier diagnosis, we have to take care of many patients with advanced or metastatic prostate cancer. Given the epidemiological and demographic data, this situation is frequently encountered in elderly men. The median overall survival of metastatic prostate cancer patients is 28–53 months, regardless of age, with only 7% of patients alive at 7 years.

Prognostic factors of survival are the initial PSA, Gleason score, volume of metastatic disease and presence of specific symptoms, particularly bone pain.

In metastatic disease, the cornerstone of treatment is androgen deprivation therapy. First-line treatment is surgical castration or medical castration by LH–RH agonists with 'flare-up syndrome' prevention or antagonists of LH–RH.

Hormone treatment should be started early and may be conducted continuously or intermittently. Patients with a normalization of PSA within 6 months are good candidates for intermittent treatment.

with disease progression, modifications of hormonal therapy can be carried out:

- Anti-androgens are used to complete androgen blockade.
- Cessation of anti-androgens since ~30% of patients derive a benefit from the anti-androgen withdrawal approach.[38,40,43]

Castration-refractory prostate cancer

Castration-refractory prostate cancer is defined in the Guidelines of the European Association of Urology:[40]

- Serum castration level of testosterone (testosterone $<50\,\text{ng}\,\text{dl}^{-1}$ or $<1.7\,\text{nmol}\,\text{l}^{-}$).
- Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with a PSA $>2\,\text{ng}\,\text{ml}^{-1}$.
- Anti-androgen withdrawal for at least 4 weeks.
- PSA progression despite consecutive hormonal manipulations.

The standard treatment of this situation is chemotherapy with docetaxel $75\,\text{mg}\,\text{m}^{-2}$ every 3 weeks combined with prednisone following the studies of Tannock *et al*.[63] and Petrylak *et al*.[64] This regimen has shown a significant benefit in overall survival and symptoms compared with chemotherapy using mitoxantrone/prednisone. The weekly administration of docetaxel has not shown the

same benefit in survival compared with mitoxantrone while symptomatic gain was found.

The survival benefit obtained with docetaxel is not influenced by patient age, as demonstrated by studies of subgroups (above and below 69 years of age). However, it is difficult to extrapolate these results to daily practice because patients in the trials represent a selected population very different from our daily practice or geriatric oncology 'routine'. In such a situation, the choice of weekly docetaxel therapy may be preferred because of better tolerance, including haematological tolerance.

Docetaxel chemotherapy feasibility, administered every week or every 3 weeks, in a population of unselected patients ≥75 years old was studied in a retrospective French study, involving 175 patients. This study confirmed good results in terms of safety and efficacy (no significant difference in terms of response on the PSA between the 3 weeks docetaxel group and the weekly docetaxel group. Overall survival reached 15 months in the global population without a significant difference between the two groups.[65]

After first-line chemotherapy, there is no standard treatment but therapies can be can be proposed to our patients such as second-line hormonal therapy (e.g. diethylstilbestrol) or second-line chemotherapy, such as docetaxel again and mitoxantrone. Second-line hormone therapy or chemotherapy is an option for symptomatic disease since no survival benefit has yet been established.

Moreover, hormone refractory bone metastasis of prostate cancer is an indication for zoledronic acid. This derives from a study by Saad *et al*. that assessed the effect of 2 years of monthly injections of zoledronic acid in patients with bone metastases from castration-resistant prostate cancer.[66] This treatment significantly increased the time to first skeletal event and reduced the rate of bone complications.

In 2010, several study results were presented and management of patients after chemotherapy with docetaxel will change in the coming months. In particular, a new taxane chemotherapy usingcabazitaxel with prednisone showed an overall survival benefit compared with mitoxantrone after docetaxel. Abiraterone, a novel anti-androgen, has also shown a significant overall survival benefit in this setting compared with placebo.[67,68]

Side effects of androgen suppressive hormones[38,40,43,57,69–71]

The side effects are frequent and many of them are generally well known to doctors and patients, such as hot flashes, lower libido and erectile dysfunction. However, other side effects have to be taken into account in elderly men.

Among them, osteoporosis is important, given the risk of fractures. Bone loss due to physiological ageing is estimated at 1–4.6% per year for men who receive androgen deprivation therapy with the risk of fracture increasing up to 45% over the long term.

Therefore, for these patients it is recommended to seek osteoporosis risk factors (family history, low weight, fracture history, alcohol abuse, smoking, use of glucocorticoids, low blood levels of vitamin D) and prescribe calcium and vitamin D. Bisphosphonates are not recommended routinely but only in cases of established osteoporosis.

In addition, hormone therapy causes an increase in fat mass and sarcopenia, which may have a very important impact in the elderly by promoting loss of autonomy, falls and fractures. Hormone therapy in prostate cancer seems also to be responsible for an increased cardiovascular risk even if the published results are sometimes contradictory. However, androgen suppression is responsible for an altered lipid profile, increase in insulin resistance and diabetes mellitus and an increased prevalence of metabolic syndrome. In some studies, such as the RTOG 92-02 study, an increased cardiovascular risk was demonstrated.

These factors are sufficient, in our view, to push clinicians to consider the cardiovascular risk in the indication of hormone therapy in elderly patients and suggest preventive measures when these treatments are needed. Already mentioned for osteoporosis, modifications of diet and lifestyle (walking, adapted diet and smoking cessation) are needed in order to reduce the metabolic and cardiovascular impact of hormone therapy.

Comprehensive care

Management of metastatic prostate cancer is not limited to the prescription of hormone therapy or chemotherapy. The patient must be accompanied throughout his disease in all dimensions of his existence: psychological and physical symptoms and social issues must be taken into account. To achieve this global care, a multidisciplinary approach is essential, as illustrated by the examples of management listed below:

- psychological and social considerations
- optimization of analgesic treatment
- possible urological intervention such as prostatic drilling
- palliative radiotherapy for bone pain or symptomatic prostate tumour
- use of radiopharmaceuticals, for multiple bone pains
- use of bisphosphonates.

Recommendations for management of elderly patients

In 2010, the International Society of Geriatric Oncology (SIOG) published guidelines for the management of prostate cancer in elderly patients.[38,43] Despite epidemiological data, very little is known about the management of elderly patients. Of course, the evaluation of health status is the cornerstone of these guidelines and experts at SIOG

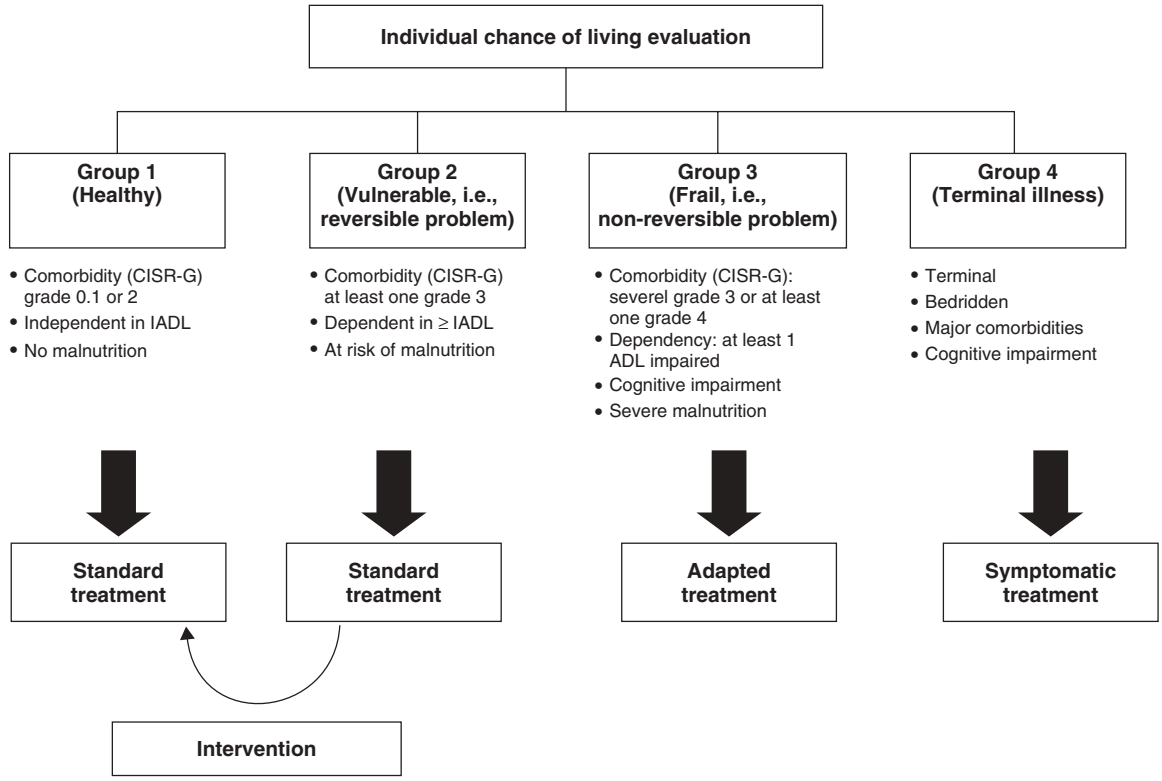

Figure 105.1 General scheme for the treatment decision-making in senior adults with prostate cancer.[38]

recommend treating patients according to their individual health status, mainly driven by their comorbidities and not according to their chronological age. In these recommendations the evaluation of individual health status is based on comprehensive geriatric assessment. This individual evaluation is necessary because of the high heterogeneity of this population. It is designed to estimate the individual probability of survival of each patient, to determine his vulnerability factors that may affect the result or tolerance of the proposed treatment and possibly offer a geriatric intervention.

The SIOG task force proposed a distribution of elderly patients into four groups, according to geriatric evaluation, focusing on comorbidities (Cumulative Illness Rating Scale – Geriatric),[72] cognitive functions (Mini Mental State Examination),[73] dependency (instrumental activities of daily living[74] and activities of daily living[75]) and nutritional status [estimated very simply by the variation (%) of weight during the last 3 months] (Figure 105.1):

- *Group 1 or 'healthy':* are able to receive standard treatment as younger patients.
- *Group 2 or 'vulnerable, i.e. with reversible problems':* may be treated as younger patients (except prostatectomy for localized disease) after geriatric intervention.
- *Group 3 or 'frail, i.e. with non reversible problems'* may receive specific but adapted treatments.
- *Group 4 or 'terminal illness'* should receive only symptomatic treatments.

This evaluation and this classification help physicians to make the best management proposal to the patient according to the medical findings and the patient's preferences

Prostatitis

Definition

The prostate is subject to various inflammatory disorders. Inflammatory or irritative conditions of the prostate were traditionally classified according to the following scheme:

- Acute prostatitis.
- Chronic bacterial prostatitis.
- Non-bacterial prostatitis, which presents with similar symptoms and signs as chronic prostatitis (including pyuria) except that cultures of urine and expressed prostatic secretions are negative.
- Prostatodynia, which also presents with similar symptoms and signs as chronic prostatitis except that the cultures are negative and pyuria is absent.

A classification approach supported by the National Institutes of Health (NIH) to standardize definitions and facilitate research made the following recommendations:[76]

• Adding an entity called asymptomatic inflammatory prostatitis.
• Combining non-bacterial prostatitis and prostatodynia into an entity called chronic prostatitis/pelvic pain syndrome.

The inflammatory subset of this syndrome included patients with significant numbers of inflammatory cells in expressed prostatic secretions, post-prostate massage urine or seminal fluid. The non-inflammatory chronic prostatitis/pelvic pain subset included the remainder of the patients with chronic prostatitis or pelvic pain.

Thus, the newer scheme defined the following categories:
1 acute prostatitis
2 chronic bacterial prostatitis
3 chronic prostatitis/pelvic pain syndrome, inflammatory
4 chronic prostatitis/pelvic pain syndrome, non-inflammatory
5 asymptomatic inflammatory prostatitis.

Manoeuvres performed in the urology office can help refine the categorization of patients. For example, including post-massage urine and seminal fluid for the assessment of inflammatory cells effectively doubles the number of people in the inflammatory subset (as compared with the older distinction using only purulent prostatic secretions).[77]

Acute prostatitis

Entry of microorganisms into the prostate gland almost always occurs via the urethra. In most cases, bacteria migrate from the urethra or bladder through the prostatic ducts, with intraprostatic reflux of urine. As a result, there may be concomitant infection in the bladder or epididymis.

Prostatitis can occur in patients with chronic indwelling bladder catheters and in those with intermittent catheterization.

Microbiology

The flora of acute prostatitis reflects the spectrum of agents causing urinary tract infection (UTI) and deeper genital infection. Gram-negative infections (typically *Escherichia coli* or *Proteus* spp.) are most common.[78] Recurrent infection after completion of therapy is usually caused by the same organism that was found in the original infection.[79]

Clinical presentation

The typical signs and symptoms of acute prostatitis include spiking fever, chills, malaise, myalgia, dysuria, pelvic or perineal pain and cloudy urine. With the exception of fever and chills, these symptoms are similar to those of lower urinary tract infection; it is important to appreciate, however, that isolated acute cystitis does not commonly occur in men, in whom virtually all lower UTIs are due to prostatitis. Men with acute cystitis often have a functional or anatomical abnormality. Swelling of the acutely inflamed prostate can cause obstructive symptoms.

Diagnosis

Clinical symptoms, together with an oedematous and tender prostate on physical examination, should prompt a presumptive diagnosis of acute prostatitis. DRE should be performed gently; vigorous prostate massage should be avoided since it is uncomfortable, allows no additional diagnostics and increases the risk for bacteraemia.

A urine Gram stain and culture should be obtained in all men suspected of having acute prostatitis. Confirmatory laboratory findings include pyuria, peripheral leukocytosis and, occasionally, positive blood cultures.

An elevated serum PSA level is also potentially consistent with a diagnosis of acute prostatitis, although a PSA should not be considered to be a standard diagnostic test for prostatitis. Elective serum PSA for prostate cancer screening should be deferred for 1 month following acute prostatitis.[80]

Treatment

A variety of antimicrobials may be used for the treatment of acute prostatitis. The barrier between the microcirculation and the prostate gland stroma limits drug entry to passive diffusion, which only permits non-protein-bound, lipophilic antimicrobial agents to reach therapeutic levels within the gland. In addition, the low pH of prostatic fluid permits antibiotics with alkaline pK_as (such as quinolones and sulfonamides) to achieve high concentrations in prostatic tissue. However, antibiotic prostatic penetration in the setting of inflammation occurs more readily. Patients with acute bacterial prostatitis may need to be hospitalized for parenteral antibiotic therapy if they cannot tolerate oral medication or if they demonstrate signs of sepsis. In such cases, shock due to Gram-negative bacteraemia may occur abruptly and be life threatening. In general, broad antibiotic coverage should be administered empirically pending the culture results.

Patients with Gram-negative rods should be treated with trimethoprim–sulfamethoxazole or a fluoroquinolone if oral therapy is indicated. Other agents with good to excellent penetration into prostatic fluid and tissue include tetracyclines, macrolides, sulfonamides and nitrofurantoin. For patients who need parenteral therapy, an aminoglycoside may be combined with intravenous fluoroquinolones. The patient should be treated as if infected with Gram-negative rods until additional culture data are available. Gram-positive cocci in chains usually indicate enterococcal infection, which should be treated with amoxicillin. Gram-positive cocci in clusters are most often due to *Staphylococcus aureus* or coagulase-negative staphylococci (e.g. *Staphylococcus epidermidis*). When *S. aureus* is recovered from a urine culture, it is important to perform blood cultures to be

certain that the bacteriuria reflects local infection and not seeding of the urine in association with bacteraemia.

Chronic bacterial prostatitis

Chronic prostatitis may present as a complication of acute prostatitis or in the absence of previously recognized initial infection. The diagnosis should be considered in men who have dysuria and frequency in the absence of the signs of acute prostatitis, in those with recurrent UTIs in the absence of bladder catheterization and in the setting of incidental bacteriuria. Gram-negative rods are the most common aetiological agent, with *E. coli* causing ~75–80% of episodes.[81] Other organisms, including enterococci, aerobic Gram-negative rods (other than *E. coli*) and *Chlamydia trachomatis* have also been associated with chronic infection.

Clinical presentation

Chronic prostatitis has more subtle clinical findings than acute prostatitis. Patients may be asymptomatic or have typical complaints of a lower urinary tract infection such as frequency, dysuria, urgency, perineal discomfort and perhaps a low-grade fever. In some cases, the diagnosis may be suspected by the incidental finding of bacteriuria. Sexual dysfunction may accompany chronic prostatitis.[82] Rectal examination may demonstrate prostatic hypertrophy, tenderness and oedema, but is frequently normal.

Diagnosis

The diagnosis of chronic prostatitis can be made by analysing specimens obtained following prostatic massage for leukocytes and bacteria. The periurethral area is cleaned and four samples are taken – the so-called four-glass test.[81] The initial 5–10 ml (VB1) and a midstream specimen (VB2) are obtained for quantitative culture. The patient should stop voiding before the bladder is empty and the prostate should then be massaged. Any prostatic secretions that are expressed (EPS) should be cultured and have a leukocyte count performed, in addition to the first 5–10 ml of subsequently voided urine (VB3). For the test to be interpretable, the colony count in VB2 must be less than 10^3 ml^{-1}, since bladder bacteriuria prevents identification of the frequently small number of organisms from the prostate. Chronic prostatitis is suspected when VB3 has more than 12 leukocytes per high power field; more than 20 leukocytes per high power field is almost diagnostic unless leukocytes were also present in VB2.

Cultures of urine or expressed prostatic secretions are almost always positive in chronic prostatitis. However, negative cultures do not necessarily exclude the possibility of bacterial prostatitis. Although the four-glass test has been described extensively in the literature, it is not clear that it is frequently used in practice. Furthermore, the results of the test apparently did not influence the use of antibiotics, since urologists who used the test routinely did not differ in antibiotic prescribing from others who used it less often. Ultrasonography may also be useful for the evaluation of prostatitis sequelae, including prostatic abscess and prostatic calcification.[83]

Treatment

Selection of agents for and duration of therapy for chronic prostatitis have not been studied using comparative trials. In cases series, there has been a general sense that various fluoroquinolone regimens have a satisfactory outcome in about two-thirds of patients who can tolerate them for >4 weeks. Failures of therapy appear to be related to underlying prostate disease, infecting agent, incomplete adherence or some other less understood component. Courses exceeding 4 weeks should be considered in patients who have previously failed treatment, who have a relatively difficult to treat organism or who cannot tolerate first-line therapy and need other agents. *Chlamydia trachomatis* should be considered in patients with clinical chronic prostatitis and negative results of urine and prostatic secretion cultures. *C. trachomatis* infection can be treated with doxycycline, azithromycin or fluoroquinolone. Chronic bacterial prostatitis often recurs and is usually treated with a second course of antibiotics. A fluoroquinolone is once again the treatment of choice.

Chronic prostatitis/chronic pelvic pain syndrome

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a clinically defined syndrome, defined primarily on the basis of urological symptoms and/or pain or discomfort in the pelvic region. Despite the use of the term 'prostatitis', it is unclear to what extent and how often the prostate is the source of symptoms.

Definitions

A number of terms have been used to describe the syndrome now commonly called chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). These include prostatodynia and abacterial prostatitis. Research guidelines define CP/CPPS as chronic pelvic pain for at least 3 of the preceding 6 months in the absence of other identifiable causes.[84]

The inflammatory subset of CP/CPPS includes patients with inflammatory cells in expressed prostatic secretions, post-prostate massage urine or seminal fluid. The non-inflammatory CP/CPPS subset includes the remainder of the patients with chronic prostatitis or pelvic pain.

Epidemiology

CP/CPPS is common. Most men diagnosed with 'prostatitis' have CP/CPPS rather than acute or chronic bacterial prostatitis. Thus, CP/CPPS is likely responsible for nearly 2 million physician visits annually in the USA.[85] In a large

population-based Canadian questionnaire study, over 20% of the men had complaints compatible with chronic prostatitis and 8–10% had moderate to severe symptoms.[77] The men with the most severe symptoms also had poorer general health and recurrent complaints.

Aetiology

The aetiology of CP/CPPS is unknown. As mentioned above, it is uncertain whether the prostate is the culprit in many cases.[86] Although bacterial infection has been suspected, particularly in the inflammatory subset of CP/CPPS, a bacterial aetiology has not been proven. Most experts believe that inflammatory and non-inflammatory CP/CPPS are both non-infectious disorders.[87] Additionally, there appears to be little correlation between histological prostatic inflammation and the presence or absence of CP/CPPS symptoms.[88]

Studies of *Chlamydia, Mycoplasma* and *Ureaplasma*, which have all been implicated in chronic prostatitis, have generally concluded that they are not responsible for CP/CPPS.[89–92] Non-infectious aetiologies have been proposed for CP/CPPS, but none has been proven. These include inflammation due to trauma, autoimmunity, reaction to normal prostate flora or some other factor, neurogenic pain, increased prostate tissue pressure and the interplay of somatic and psychological factors. Psychological stress appears to be common in men with symptoms of CP/CPPS.

Clinical manifestations

The clinical presentation of CP/CPPS can be similar to that of chronic bacterial prostatitis (frequency, dysuria, perineal pain). To meet the NIH consensus definition, patients should not have active urethritis, urogenital cancer, urinary tract disease, functionally significant urethral stricture or neurological disease affecting the bladder.[76]

Diagnosis

The symptoms of prostatitis are common and often not recognized by physicians. These symptoms include pain (in the perineum, lower abdomen, testicles and penis and with ejaculation), bladder irritation, bladder outlet obstruction and sometimes blood in the semen. Impotence is occasionally attributed to prostatitis; however, it occurs no more commonly than in men of a similar age without prostatitis. CP/CPPS is a diagnosis of exclusion and the evaluation is designed to rule out identifiable causes of pelvic pain:

- On physical examination, patients should be evaluated for hernias, testicular masses, rectal masses and haemorrhoids. Patients with CP/CPPS are typically afebrile. On rectal examination, the prostate is usually not tender but may sometimes be mildly tender; severe tenderness suggests acute prostatitis.
- A urinalysis should be performed.[93] Patients with haematuria should have an evaluation that includes urine cytology (looking for carcinoma *in situ* of the bladder), cystoscopy and upper tract imaging with intravenous pyelography or computed tomography scan.
- A urine culture is required to rule out UTI.[93] Patients with recurrent UTIs should be evaluated for chronic bacterial prostatitis.
- In patients who report a sensation of incomplete emptying of the bladder, a post-void residual should be checked by catheterization or ultrasound.

The classic four-glass test is no longer routinely performed. A PSA test is not indicated and if PSA is measured and found to be elevated, the elevation should not be ascribed to CP/CPPS.[94]

Imaging studies are appropriate in some patients. Patients with concomitant abdominal pain may require imaging with CT to exclude an intra-abdominal process. Testicular pain should be evaluated with a scrotal ultrasound. Lumbar radiculopathy can produce pelvic pain, so patients with signs and symptoms suggesting this diagnosis (e.g. lower extremity paraesthesias or weakness) may require imaging of the spine with magnetic resonance imaging.

In primary care practice, patients suspected of having acute or chronic bacterial prostatitis will frequently receive an empirical trial of an antibiotic and the diagnosis of CP/CPPS will only be entertained in those patients who relapse or do not respond to such therapy.

Treatment

A number of therapies have been tried for CP/CPPS; however, there is no uniformly effective treatment. One group attempted a meta-analysis to examine diagnostic testing and treatments but found substantial methodological problems with the studies assessed.[95,96] The NIH developed a chronic prostatitis symptoms index that was validated and can be used to evaluate different treatment measures.[97] In addition to the validation set of referral patients to the NIH, this symptom index has also proven useful in the assessment of patients presenting to general medicine and urology clinics. The maximum possible symptom score is 43, where higher numbers indicate more severe symptoms.

Antibiotics

Randomized trials in men with CP/CPPS have not found significant benefits with quinolone antibiotics.[98,99]

α-Blockers

Even in the studies showing benefit with α-blockers, the overall decrease in symptom scores was small and likely of only marginal clinical significance. Given the evidence showing a lack of benefit, we recommend not treating pain attributed to CP/CPPS with α-blockers.[100–104] Since the

NIH–CPSI score focuses mainly on pain, it remains possible that α-blockers could improve urinary symptoms in men with CP/CPPS. A trial of α-blockers in men with CP/CPPS and troublesome urinary symptoms is reasonable.

5α-Reductase inhibitors

Randomized trials of finasteride in men with CP/CPPS have suggested possible small benefits.[101,105] The degree of clinical benefit was not sufficient to warrant the routine use of 5α-reductase inhibitors in men with CP/CPPS who do not have another indication such as benign prostatic hyperplasia.[101]

Anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) may be of some benefit in controlling symptoms in men with CP/CPPS. A randomized trial found a trend towards benefit with rofecoxib compared with placebo, particularly at higher doses.[98] Rofecoxib is no longer available, but non-selective NSAIDs can be tried for symptomatic control.

Other

A number of other treatments have been tried for CP/CPPS: pollen extract or saw palmetto does not appear to be effective; a small study suggested that transurethral needle ablation of the prostate is no more effective. Sitz baths may provide some pain relief. Psychotherapy has been recommended if there is sexual dysfunction. Physical therapy aimed at achieving myofascial trigger point release may have benefit in some patients.[106]

Key points

- Benign prostatic hypertrophy (BPH), cancer and prostatitis are the three main conditions affecting the prostate gland in older men.
- BPH is a major contributing factor in the development of LUTS – lower urinary tract symptoms.
- Prostate cancer is an extremely frequent malignant disease. It represents the second most common cancer in men after lung cancer and the fifth cause of death by cancer in the world.
- Clinical symptoms, together with an oedematous and tender prostate on physical examination, should prompt a presumptive diagnosis of acute prostatitis.

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CHAPTER 106

Urinary incontinence

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Introduction

Urinary incontinence (UI) is defined as an involuntary loss of urine in sufficient amounts or frequency as to constitute a medical, hygienic, or psychosocial problem. It is not a single disease, but the clinical manifestation of a diverse set of pathophysiological mechanisms, which must be understood in order to provide optimal management. In its mildest form incontinence may present as an occasional dribbling of small amounts of urine – an inconvenience to which the patient may adapt well. In severe cases it is a potentially devastating condition with serious health consequences. It is associated with significant functional decline and frailty resulting in increased risk of institutionalization and even death. In community-dwelling elderly with progressive debility, UI is cited as a leading factor resulting in nursing home placement.[1]

The prevalence of UI increases with age and frailty. It is up to twice as common in women than in men. Reports of prevalence vary greatly and depend on the definition and degree of incontinence, the method of investigation, and the target population studied. Approximately 1 in 3 women and 1 in 5 men over the age of 65 years have some degree of incontinence, and 5–10% of community-dwelling elderly experience sufficient incontinence as to require modification of lifestyle and/or use daily incontinent pads.[2] By the age of 80 years, 15–40% of community-dwelling elderly have experienced incontinence.[3] In nursing home residents, the prevalence increases to 60–80 %.[4] Despite the high prevalence of UI in the elderly, and its profound impact on quality of life (QOL), UI continues to be under-reported and under-diagnosed. The reluctance of both patients and providers to address the problem is due, in part, to the stigma associated with incontinence and the false belief that it is an unavoidable consequence of ageing.[5,6] Despite great strides that have been made in dissociating social stigma from a variety of diseases (e.g. acquired immune deficiency syndrome and sexually transmitted diseases), UI continues to suffer from a negative stereotypical bias, which hinders a frank discussion of the problem at the primary care level and therefore delays timely intervention (Table 106.1). It is estimated that 50–70% of incontinent persons do not seek help for their problems,[7,8] and in a survey of primary care physicians, the majority enquired about incontinence in 25% or fewer of their patients.[9] For these reasons, it is essential that questions about incontinence be included in the routine assessment of every older patient.

Pathophysiology and types of urinary incontinence

Normal bladder control is a complex process that depends on a functional autonomic and somatic nervous system, sufficient cognitive and physical function, and an adequate environment. Multiple pathological mechanisms exist, both age-related and disease-specific, that result in the various types of incontinence. Age alone, however, is not a necessary factor in the development of urinary incontinence, nor is UI a normal consequence of ageing. Bladder relaxation is a physiologically active process under sympathetic (adrenergic) control. Voiding, which consists of detrusor contraction with relaxation of the internal urethral sphincter, is mediated by the parasympathetic (cholinergic) system. Parasympathetic nerves act directly on the detrusor muscle, as well as by inhibiting sympathetic tone. Normal bladder capacity ranges between 250–600 ml. In most simplified terms, during bladder filling afferent autonomic sensory pathways carry information on bladder volume to the sacral micturition centre. Sympathetic output inhibits parasympathetic activity, relaxes the detrusor muscle, and constricts the internal urethral sphincter, thus allowing the bladder to fill. Normally, intravesicular pressure remains low as the bladder actively distends. Once bladder volume reaches approximately 50% bladder capacity, the first urge to urinate occurs and sensory impulses are sent to the detrusor motor centre in the pons. Frontal lobe neurons exert

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 106.1 Reasons for under-reporting and under-management of urinary incontinence.

Patient-related concerns

- Persons with incontinence are ashamed or embarrassed about their condition.
- Persons with incontinence are in denial.
- Persons with incontinence have fear of stigmatization.
- Insidious onset and long trajectory course allows older persons to adapt to incontinence.
- The elderly believe incontinence is an inevitable consequence of ageing.
- Patients believe that nothing can be done for incontinence.
- Patients fear that surgery is necessary to cure incontinence.
- Elderly patients prioritize health conditions, and incontinence is viewed as an inconvenience compared to more serious conditions.
- Lack of appropriate communication and encouragement from healthcare provider.
- Patients with incontinence fear impending institutionalization.

Provider-related concerns

- Provider is uncomfortable managing incontinence.
- Absence of routine screening.
- Providers prioritize other complaints due to time constraints.
- Provider views incontinence as sign of other conditions being addressed.

a predominantly inhibitory influence on pontine activity, which allows for suppression or delay of urination. Similarly voluntary contraction of pelvic floor musculature, including the external sphincter, inhibits parasympathetic tone, as occurs when urination is interrupted in mid-stream. Once conditions are appropriate to urinate, conscious disinhibition of parasympathetic outflow is initiated. Disorders of the cerebral cortex such as stroke, dementia, or Parkinson's disease or spinal cord injury can interfere with these pathways and cause incontinence.

In addition to the aforementioned conditions, several age-related changes challenge the lower urinary tract control mechanisms in the elderly. Diminished detrusor compliance effectively decreases bladder capacity, and when combined with impaired bladder contractility, urinary frequency and urgency results. Urethral pathology can further compound the problem. The urethra measures approximately 18–22 cm in men and 4 cm in women. Anatomic urethral obstruction in men due to prostatic enlargement, and urethral incompetence in women due to urethra shortening or sphincter weakness are common age-related problems. Increased nocturnal urine production can occur due to blunting of the circadian rhythm of arginine vasopressin[10] and reabsorption of leg oedema resulting from venous insufficiency, heart failure, or low serum albumin levels. Other common geriatric conditions associated with increased risk if UI are polyuria due to uncontrolled hyperglycaemia, hypercalcaemia, constipation and frailty. Impaired cognitive function and functional decline may precipitate incontinence as a manifestation of global decompensation. Available data suggests that cerebrovascular disease increases the risk of developing UI in older women by as much as twofold.

Based on those mechanisms, urinary incontinence is classified into four groups (Table 106.2).

Urge incontinence

Urinary urgency with or without incontinence affects 1 in 4 adults over the age of 65 years. It is the most common cause of UI in the elderly and accounts for up to 70% of all cases of incontinence. Urge incontinence is characterized by an insuppressible urge to void resulting in loss of urine, sometimes in large amounts (>100 ml). Clinically, patients with urge incontinence will typically have a sudden strong urge to void, fear of leakage, inability to suppress the urge, and not enough time to get to the bathroom. This type of incontinence is often associated with neurological disorders, such as stroke, spinal stenosis, Parkinson's disease, or dementia. The terms 'overactive bladder', 'detrusor hyperreflexia', and 'detrusor instability' have sometimes been used interchangeably. All result in urge incontinence, but strictly, detrusor hyperreflexia is reserved for conditions in which a neurological problem is identified; if no neurological disorder is present, detrusor instability is the proper term. Not all cases of urge incontinence are associated with involuntary detrusor contractions, however. A subtype of urge incontinence is detrusor hyperactivity with impaired contractility, in which incomplete bladder emptying occurs due to involuntary contractions, resulting in high postvoid residuals. This condition can mimic overflow incontinence and the diagnosis may require urodynamic testing. Establishing the proper diagnosis is of critical therapeutic importance, since treating urge incontinence misdiagnosed as overflow can worsen symptoms. Detrusor overactivity with impaired contractility frequently occurs in conjunction in patients with diabetes mellitus, and is sometimes classified under the separate category of *mixed incontinence*.

Stress incontinence

Stress incontinence occurs more often in women than men in all age groups. It is the involuntary loss of urine, usually in small amounts, with increased intra-abdominal pressure such as occurs during coughing, sneezing, lifting, or laughing. Stress incontinence accounts for approximately 25% of all cases of all UI in women. It has multiple anatomic and pathological causes but the underlying common mechanism is incompetence of bladder outlet support tissue. This may include urethral sphincter weakness, atrophy of pelvic

Table 106.2 Clinical presentation in types of incontinence.

Symptom	Urge	Stress	Overflow	Functional
Urgency	yes	no	no	variable
Leakage with straining	no	yes	variable	no
Volume leaked	large	small	small	large
Strength of urine stream	variable	normal	weak	normal
Nocturia	yes	no	variable	yes
Ability to reach toilet in time	reduced	normal	normal	reduced
Bladder distention	no	no	yes	no

floor musculature, hypermobile urethra, or disruption of the angle between bladder neck and urethra. Risk factors include vaginal childbirth, hysterectomy, lack of estrogen and obesity. In advanced cases, large amounts of urine loss may occur with minimal strain, such as during change in posture from sitting to standing, and may render the person housebound.

Overflow incontinence

While urge and stress incontinence primarily involve problems with storing urine, the hallmark of overflow incontinence is a failure to properly empty the bladder. This can be due to increased bladder outflow resistance or a poorly contractile bladder, or both. Common causes include prostatic enlargement, urethral stricture and neuropathic bladder due to diabetes. Less common but potentially treatable causes may include bladder prolapse, spinal injury or stenosis, or pelvic masses such as uterine fibroids. Incontinence occurs when the build-up of intra-vesicular pressure in an overdistended bladder finally exceeds that of outlet resistance. Patients with overflow incontinence report trickling of urine, usually in small amounts, in the presence of suprapubic fullness. Additional symptoms include urinary frequency, hesitancy and urgency, as well as a weak urine stream, nocturia and postvoid dribbling. Urine loss with increased intra-abdominal pressure may mimic stress incontinence, except for the differentiating sign of an uncomfortably distended bladder. Medications with strong anticholinergic or α-agonist effects are rarely the sole cause of overflow incontinence, but can exacerbate mild or subclinical cases, and may cause complete obstruction in more advanced stages.

Functional incontinence

Functional incontinence occurs when a patient is unable or unwilling to access toilet facilities in time to void. Factors include musculoskeletal problems, neurological problems, advanced dementia, psychological problems, physical restraints and frailty. Iatrogenic aetiologies include overuse of sedatives or hypnotics, restricting mobility and use of restraints and barriers. Implicit in functional incontinence is that the problem lies outside the lower urinary tract. However, patients with functional incontinence due to any of above factors will almost certainly also have abnormalities affecting the lower urinary tract, and it is sometimes difficult to determine where the predominant problem lies.

Complications and impact of incontinence

Medical complications of urinary incontinence are varied and have been well documented. Aside from the natural progression of the underlying condition causing incontinence, incontinence itself may result in potentially serious complications. In women over the age of 65 years, there is a significant increase in the incidence of traumatic falls associated with incontinence. Up to 40% of women with UI will fall within a year, 10% of which will result in fractures. Acute hospitalization, institutionalization and social isolation have all been associated with UI in older patients. Thirty percent of incontinent women over the age of 65 years are likely to be hospitalized within 12 months.[11] In older men, the risk of hospitalization associated with incontinence is double. Pressure ulcers are more prevalent in frail incontinent patients, as are skin infections, balanitis and cystitis. Not surprisingly, the economic cost of urinary incontinence can be extremely burdensome on affected individuals and long-term care facilities. The cost of care for UI is difficult to determine with accuracy due to the wide-ranging and overlapping nature of this condition. It is estimated that the annual direct cost of managing UI in the US exceeded US$20 billion in 2004.[12] Birnbaum *et al*. estimated the lifetime medical cost of treating an older adult with UI at close to US$60 000,[13] and long-term care facilities shoulder an additional annual financial burden of approximately US$5000 per resident with incontinence. None of this direct cost accounts for reduced work productivity, loss of self-esteem, or caregiver burden and burnout.

The psychosocial impact of UI continues to receive less attention than it commands, despite the inescapable effect

on the QOL of affected persons. Great strides have been made in the past 20 years in developing and validating psychosocial assessment tools specifically for incontinence, but UI continues to be viewed by clinicians as a unidimensional medical condition. The impact of a potentially chronic non-life-threatening disease is highly subjective and varies greatly among individuals and even within the same individual over time. It is influenced by cultural, social and psychological factors, as well as the personal concept of self-image, self-worth and health expectations. These human experiences are difficult to measure, but are important nonetheless, because they not only determine the patient's willingness to seek professional help, but also their ability to adapt to the situation and benefit from treatment. A failure to identify the broader consequence of UI is to deny comprehensive management of this complex condition. Even if the underlying condition is incurable, much can be done to alleviate the psychosocial anguish that may accompany UI. Multiple condition-specific and dimension-specific QOL questionnaires have been devised for this purpose and are summarized elsewhere.[14] These tools have also been proven an invaluable component of clinical research, particularly in outcome studies.

Diagnosis and assessment of urinary incontinence

Given the strong intrusion of UI on everyday life, one might assume that incontinent persons would seek help early and often. This is not the case. Although up to 70% of incontinent patients do not freely report the problem, more than 75% will report the condition when asked by their physician.[15] Symptom reporting tends to be marginalized or minimized because of insecurity, fear of hostile distancing, or stigmatization (Table 106.1). In one study, only approximately one third of women with incontinence reported it as bothersome,[16] and 60% of people identified through surveys as being incontinent had not reported their condition to a healthcare provider.[8] When medical attention is sought, it often is after symptoms have been present for a long time, sometimes years, and there is almost complete failure of the underlying physiological regulatory or compensatory mechanisms. The onus lies within providers to screen for UI and identify risk factors in all patients being evaluated.

The objective of the initial evaluation is to identify potentially reversible causes of incontinence (particularly in cases of acute-onset), to classify incontinence in order to devise a treatment plan, and to identify conditions that warrant surgical intervention. In most cases, a detailed history and physical examination suffices to formulate a working diagnosis and guide initial therapy (Table 106.2). The history should cover characteristics of voiding and incontinent episodes, concurrent medical problems of relevance, and an assessment of QOL and caregiver burden. Special attention should focus on quantity of urine loss, duration of the problem, frequency and urgency, as well as strength of the urine stream, dribbling, dysuria, nocturia and leakage during activity. When indicated, inquiry should be made regarding diabetes mellitus, neuromuscular disorders, pelvic surgery, childbirth, cognitive and functional impairment, and alcohol/coffee/fluid intake. Presence of specific risk factors can add support to an uncertain diagnosis, and guide further investigation. A detailed list of prescription and over-the-counter medications should be made, and any temporal association between symptom onset or exacerbation and medication use (or stoppage) should be noted. Many commonly used medications contribute to incontinence (Table 106.3), and surreptitious, casual, or impulsive use of non-prescription medications should be investigated. As with most chronic conditions, the outcome and tolerance of previous treatment attempts can be of immense value in formulating a current treatment plan. An incontinence diary is an important tool when classification of incontinence remains unclear and further information is necessary. Repeat or serial diaries also facilitate assessment of intervention outcome and are often more accurate than the patient's subjective report from memory. A seven-day diary, or longer, may be necessary for infrequent episodes of incontinence, but a shorter 2–3 day voiding diary appears to be comparable in reliability and validity when incontinent episodes are more frequent. Furthermore, patients are more likely to comply with the shorter diary, as they perceive it as being less burdensome and intrusive.[17]

Physical examination of patients with UI should include an abdominal, neurological, rectal and pelvic examination. Abdominal examination does not reliably detect elevated postvoid residuals until urine retention exceeds 500 ml. An overdistended bladder can usually be detected by palpating or percussing the suprapubic area, and will often be uncomfortable to deep palpation. Similarly, prostate size on digital rectal examination does not correlate well with symptoms of bladder outlet obstruction and overflow incontinence. However, valuable information regarding prostate nodules, symmetry and tenderness, as well as rectal tone and reflex tightening of the anal sphincter with coughing renders this examination essential. Pelvic examination in women should include inspection for prolapse, infection and atrophic vaginitis. Clinically significant prolapse of the uterus, bladder, urethra, or intestine warrants prompt referral to specialist for consideration of surgical and non-surgical modalities to relieve the obstruction. During pelvic examination, a cough test should be performed for stress incontinence. Patients with intact perineal sensation and reflexes will exhibit reflex tightening of the anal and urethral sphincter tone during coughing. Persons with stress incontinence may be observed leaking urine while

Table 106.3 Examples of common medications and substances that can worsen incontinence.

Medication class	Possible effect	Type of incontinence most affected
Alcohol	Polyuria, impaired mobility	Overflow, stress, functional
Caffeine	Polyuria, bladder irritant	Stress, urge, overflow
Smoking	Bladder irritant, cough	Urge, stress
Antihistamines	Urine retention, increased urethral tone, decreased bladder contraction	Overflow
Diuretics	Polyuria	Urge, overflow, stress
Alpha-adrenergic blockers	Decreased bladder outlet resistance	Stress
Alpha-adrenergic agonists	Increased bladder outlet resistance Urine retention	Overflow
Opiate analgesics	Sedation, decreased detrusor activity, increased bladder outlet resistance, urine retention	Overflow, functional
Tricyclic antidepressants	Urine retention, increased urethral tone, decreased bladder contraction	Overflow

coughing. Loss of urine during coughing is highly specific for stress incontinence, but can also occur in overflow incontinence, and the absence of a positive test does not rule out stress incontinence. Finally, a comprehensive assessment of UI should include evaluation of cognitive impairment and mobility, and the role each may have in causing or worsening incontinence.

Few diagnostic tests are necessary in the workup of urinary incontinence. In most cases, a urinalysis is performed to look for infections, haematuria and glucosuria. Cytology and imaging tests are only indicated if unexplained haematuria is present. With the exception of infections, urinalysis rarely is expected to assist in the diagnosis or alter the management of incontinence. In fact, guidelines of various agencies, including those of the American Medical Director Association, recommend urinalysis only in cases of suspected infection or with worsening symptoms.[18] It may be prudent, however, to obtain a urinalysis during the initial workup of new incontinence, particularly if symptoms developed acutely or progressed rapidly. Overt urinary tract infections are clearly associated with acute urinary incontinence, but the role of asymptomatic bacteriuria on incontinence is much less clear. In frail elderly patients with chronic stable UI, such as nursing home residents, treatment of asymptomatic bacteriuria is not advised. It is reasonable to initiate a course of antibacterial therapy when clinical symptoms of infection develop, or during initial management of incontinent patients with bacteriuria. Urinary stasis dramatically increases the risk of asymptomatic bacteriuria as well as acute symptomatic cystitis, particularly when bladder catheterization is necessary. In poorly controlled diabetes mellitus, the diuretic effect of hyperglycaemia worsens most types of incontinence. Additionally, autonomic neuropathy of diabetes can worsen urinary urgency and urine retention. Measurement of postvoid residual (PVR) performed by bedside ultrasound bladder scan or by in-and-out catheterization is effective in diagnosing urine stasis and consequently overflow incontinence. Not all patients require PVR assessment. Only patients at high risk for urine retention should have a PVR measurement. Symptoms and physical examination are poor and unreliable predictors of urine retention. Normal postvoid residual volume in older patients is less than 100 ml. A PVR volume of 200 ml or more strongly indicates urinary retention, and is consistent with either outlet obstruction or atonic bladder. Volumes between 100 ml and 200 ml are difficult to interpret but at least suggest inadequate bladder emptying. Portable ultrasound scan is preferred to urethral catheterization for PVR measurement. It is non-invasive and highly reliable when performed by a competent operator. Bladder catheterization carries the risk of infection and urethral trauma, even with a single in-and-out event, but has the therapeutic advantage of draining an overdistended bladder. In severe cases of retention, the catheter may remain in place until a long-term treatment plan is devised.

Most incontinent patients will not require further workup, but when the type of incontinence remains uncertain after the initial assessment, referral for formal urodynamic studies must be considered. Patients that may benefit from urodynamic studies include those with competing pathological mechanisms, history of pelvic surgery or radiation therapy, treatment failure, and those being considered for surgery. Bedside cytometric studies are no longer done mainly due to poor diagnostic accuracy and failure to modify management based on clinical criteria. Furthermore, bedside cytometric studies correlated poorly with formal urodynamic studies.

Management of urinary incontinence

Effective management of persistent incontinence will generally incorporate elements of both non-pharmacological

and pharmacological strategies. Traditionally, pharmacological therapy was withheld until non-pharmacological strategies proved ineffective. Some experts, however, have suggested that a parallel approach to therapy may yield better results.[19] Nevertheless, the risk of adverse drug effects and polypharmacy justifies caution in starting medications without fully appreciating other modalities in older patients.

Non-pharmacological modalities

Several non-pharmacological interventions have been used for the management of UI with varying degrees of success. The modality choice and goal of treatment varies with the type of incontinence. Degree of incontinence and comorbid conditions also determine optimal treatment plan. Options include supportive management, including the use of protective undergarments, bedding and topical barrier creams, intended to manage rather than treat incontinence, as well as more involved measures such as behavioural intervention aimed at modifying the progression and impact of the disease. Several studies have shown behavioural modification to be comparable to drug therapy in alleviating symptoms, particularly for stress and urge incontinence. Patient-dependent behavioural therapy is intended to restore continence, and requires the patient to have functional independence, cognitive competence and, above all, motivation. When patients are unable or not willing to participate, caregiver-dependent toileting protocols are more appropriate and are effective in maintaining a hygienic and safe environment, and minimizing incontinent episodes. Neither supportive care, nor behavioural modification address the underlying pathogenic process, except, perhaps, in the case of stress incontinence secondary to bladder outflow incompetence where perineal strengthening exercises may retard the natural progression of the disorder, and in some cases of urge incontinence where biofeedback may actively inhibit bladder contractions.

Rehabilitation exercises of pelvic muscles with biofeedback therapy may prove highly effective in patients with stress or mixed incontinence. Pelvic floor exercises, such as the Kegel exercise, consist of repetitive contraction and relaxation of pelvic floor muscles, a manoeuvre somewhat opposite to that of the Valsalva manoeuvre. The success of pelvic muscle exercises is dependent on a knowledgeable and committed instructor. In addition, biofeedback is helpful in identifying the proper muscle group during initial training, particularly in patients who tend to bear down which is a more natural manoeuvre but may trigger leakage in stress incontinence. It was estimated in one study that only about half the patients who received only verbal instructions on pelvic floor muscle exercises were able to perform the technique properly.[20] Biofeedback can be electronic-based using intra-vaginal pressure transducers and computer feedback, or more simply by manual sensation during the rectal or vaginal examination. Once learned, the frequency and duration of contractions can be increased, and the manoeuvre should be performed several times a day. Highly motivated persons can be trained to perform the contraction with activities that precipitate leakage during their daily routine, such as laughing or sneezing.

In functionally dependent or cognitively impaired patients, *prompted voiding* is likely to be more effective. It is a caregiver-dependent strategy that offers the patient regular opportunities to void by asking about the need to use the restroom and providing assistance and encouragement at routine intervals, usually every two hours during the daytime. Positive reinforcement and social interaction are additional benefits, but clearly a dedicated caregiver is necessary for this approach to succeed. *Habit training* is a variant of prompted voiding, in which the encouragement to void is linked to specific daily activities, such as meals, bathing, or naptime, rather than routine predetermined intervals. The intent is that with continued training, a *habit* to address toileting needs develops with these frequent daily activities. The variability of this approach allows the schedule to be personalized to the patient's daily habits and routine. With more advanced dementia, *timed (or scheduled) toileting* consists of routinely toileting a patient at fixed intervals, whether or not he/she expresses a need to void. This labour-intensive process is dependent on staff or caregiver availability and dedication, and in long-term care facilities may be constrained by the regimented schedule of custodial care. Furthermore some patients with advanced dementia will resist routine toileting, and agitated behaviour may ensue.

Pharmacological management

Detrusor contractility is primarily dependent on activation of the muscarinic acetylcholine receptors. Consequently, anticholinergic agents have been the mainstay of treatment for patients with urge incontinence. This class of drugs can be quite effective. Various studies estimate a 50–70% reduction in the frequency of incontinent episodes in older patients with urge incontinence treated with antimuscarinic agents.[21] Drug selection, however, is based on efficacy as well as tolerability, and this class of medications has been plagued by an unacceptable high frequency of intolerable side effects such as dry mouth, constipation, blurred vision, cognitive dysfunction, delirium and orthostatic hypotension. Five subtypes of muscarinic receptors (M1-M5) have been identified in the central nervous system and peripheral organs. The receptors differ in end-organ targeted, as well as their capacity for activation or inhibition by certain molecules. Systemic effects of anticholinergic drugs are linked to receptor selectivity, and until recently, prohibitive

side effects of non-selective drugs rendered them of limited use in older adults. Oxybutinine and tolterodine are the most widely used drugs for the management of urge incontinence in the United States. Oxybutinine, has been shown to reduce incontinent episodes by half in most patients with urge incontinence, but also has a high rate of discontinuation due to side effects. It is an older medication with antagonistic effect on the M1, M2 and M3 acetylcholine receptors, and hence not highly selective in activity or effect. Approximately 75% of patients on oxybutynin will experience bothersome side effects, and 25% will discontinue the medications due to peripheral anticholinergic effects.[22] Tolterodine appears to be comparable to oxybutynin in efficacy. It affects predominantly the M2 and M3 receptor subtypes, and therefore has a more favourable tolerance profile. Sustained release formulations of both drugs are favoured over the immediate release due to simplicity of dosing and better tolerability. More recently, oxybutynin transdermal patch and 10% gel have been approved in the United States for urge or mixed incontinence. Oxybutinine is also the only antimuscarinic available in generic form. The cost benefit is the primary reason for initiating treatment with a trial of this drug.

In 2004, the Food and Drug Administration (FDA) approved solifenacin and darifenacin in the United States for treatment of urge incontinence. These drugs are more selective muscarinic receptor inhibitors (M3), and appear to be at least as effective as tolterodine and equally well tolerated. It is not yet clear, however, whether increased receptor selectivity translates to better tolerability. In a three-month randomized trial of 1200 adults, dry mouth and constipation occurred *more* frequently with solifenacin than with tolterodine (30 vs 24, and 6 vs 3 respectively), thought the difference was not statistically significant.[23] Also in 2004, trospium was approved by the FDA in the United States for the management of OAB. Trospium has been used effectively in Europe for over three decades, and accumulated literature indicate a favourable safety profile. Unlike the M2/M3 selective agents that are lipophilic tertiary amines, trospium exhibits less receptor selectivity but is a hydrophilic quaternary amine. This biochemical property renders it relatively impermeable to the blood-brain barrier and hence limits unwanted central nervous system side effects. Trospium is not metabolized by the cytochrome p450 system and so is less prone to drug interaction. Renal excretion accounts for approximately 70% of drug clearance, and in older patients with renal impairment it must be dosed accordingly. As with other antimuscarinic drugs, the extended release formulation was better tolerated than immediate release in one small study.[24] With current data, there is no compelling evidence that among selective antimuscarinics, any one is vastly superior to another in efficacy or tolerability. In one large study, discontinuation rate for this class of medication was 58–71% at six months.[25]

All patients on antimuscarinic drugs should be monitored for urine retention, particularly older males with potential prostate enlargement. Postvoid residuals should be measured, and when retention is present, dose reduction or discontinuation of drug altogether may be necessary. In older men with bladder outflow obstruction, alpha-adrenergic antagonist treatment prior to starting antimuscarinic agents may reduce the complication of problematic urine retention.

Pharmacological management of stress incontinence has been far less rewarding than urge incontinence. Estrogen has a direct effect on urethral mucosa. Postmenopausal women experience a loss of periurethral tissue, diminished mucosal blood flow, and decreased number and responsiveness of alpha-receptors. On pelvic examination of postmenopausal women, dry, inflamed, friable, or dusky-coloured mucosa with loss of rugae suggests atrophic vaginitis. Hence, intuitive reasoning has driven estrogen to the forefront of treatment options for stress incontinence in older women. In fact, estrogen replacement therapy, both topical and systemic, has been widely used for decades, despite the absence of compelling evidence of efficacy. Vaginal estrogen in the form of creams, tablets, or medicated rings can decrease the frequency of recurrent cystitis and alleviate dyspareunia. Anecdotal evidence suggests improvement in symptoms of stress and mixed incontinence, but a recent large prospective cohort study found that vaginal estrogen cream in women 55–75 years of age was independently associated with incident incontinence during two years of follow-up (OR, 2.0; CI, 1.1–3.7).[26] When effective, several months of therapy is necessary to notice clinical improvement, and patient inconvenience or embarrassment may limit the duration of treatment. Oral conjugated estrogen, with and without progesterone, has been better studied and is no more effective than topical estrogen. In fact, in the Women's Health Initiative (WHI) study of over 23 000 subjects, women who were continent at baseline had an increased risk for all types of incontinence at one and three years follow-up compared to placebo.[27] The greatest increase in risk was for stress incontinence. Women who were incontinent at baseline had worsening incontinence and frequency with treatment. These results have been replicated in other large controlled trials, such as the Heart and Estrogen/Progestin Replacement Study,[28] and Nurses' Health Study,[29] though the latter only included younger subjects. Based on the existing evidence, estrogen is not recommended, or approved, for the treatment of stress incontinence.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor that has been approved in Europe since 2004 for the treatment of stress incontinence. It affects the lower urinary tract function via alpha-adrenergic central nervous

system mechanisms. Despite evidence for improvement in QOL and a moderate decrease in frequency of incontinence compared to placebo,[30–32] the Cochrane Collaboration in 2005 and University of Minnesota review in 2008 independently concluded that cure rates with duloxetine were no better than placebo. In addition to the modest transient therapeutic effect, potentially serious side effects have further deterred clinicians from utilizing this drug for incontinence. In the United States, duloxetine is approved for major depressive disorder, but recently failed to gain FDA approval for the treatment of incontinence.

Surgical management

For patients who respond poorly to behavioural and pharmacological interventions surgical procedures may prove effective. Age *per se* is not a contraindication for surgical consideration; however, comorbid conditions, which accrue with age, are. As with any surgery in older persons, patient selection and preparation are paramount. Since mixed incontinence is not uncommon with advancing age, urodynamic studies must be performed in patients being considered for surgery. This procedure delineates the underlying pathological mechanism(s), and allows better prognostication of postsurgical course.

Surgery should be considered in women with urine retention due to pelvic prolapse that has failed conservative measures. Surgery is also a well-accepted treatment choice for stress incontinence. Minimally invasive procedures for bladder outlet incompetence include bladder neck suspension, periurethral collagen injections, and tension-free vaginal tape (TVT). Mid-urethral synthesis slings (TVT) can be used as a first-line treatment in older women with stress incontinence. The TVT sling procedure is a 30-minute outpatient procedure and has a cure rate above 85%. Refractory cases will require the more invasive wide sling procedure rather than a simple bladder neck suspension. The varied procedures are intended to restore the 90° angle between the urethra and bladder neck, and provide bladder support in case of prolapse. Complications include bladder perforation, urine retention, haematoma/thrombosis, and infection. Periurethral bulking injections with collagen and other agents provides mechanical resistance by external compression of the urethra, and is an alternative to traditional surgery when the urethra is immobile.

Electrical stimulation has been used in urge incontinence refractory to medical treatment. External sacral nerve stimulation via cutaneous electrodes in the lower back is safe and can be effective. If significant improvement in symptoms is noted with a trial of external stimulation, a permanent device can be implanted. This 'bladder pacemaker' is placed in the hip or gluteal area, and a lead wire within the sacral canal stimulates the pudendal and sacral nerves. External programming results in the delivery of a painless electrical stimulus, which regulates bladder function. Initial reports have indicated promising long-term results.[33]

Key points

- Urinary incontinence is a very common problem in older persons.
- Mixed incontinence is common, making treatment difficult.
- Lower urinary tract symptomatology occurs in both men and women and is not directly related to prostate size.
- Nocturia is a common problem especially in older males.

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CHAPTER 107

Geriatric nephrology

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Introduction

The border between normal ageing and disease is sometimes blurred because the ageing process consists of a loss of *complexity*, as a result of which the different systems of a senile organism start working without harmony among them, a situation that predisposes to clinical alterations and disease. The kidney also is under this general rule of the ageing process. The discipline of geriatric nephrology includes the normal renal ageing changes, their clinical consequences, and the renal diseases that occur in the elderly population as a result of these changes.[1]

Normal ageing: Glomerular level

Decrease in glomerular filtration (senile glomerulosclerosis)

In senile glomerulosclerosis, the glomeruli are replaced by fibrous tissue (glomerular obsolescence), a process that begins at approximately 30 years of age, and is present in between 1% and 30% of persons aged 50 years or older. The mesangium increases to nearly 12% by age of 70, and microangiographic examination shows the obliteration particularly of the juxtamedullary nephrons that is followed by the formation of a direct channel between afferent and efferent arterioles (*aglomerular circulation*). Presumably, this change contributes to medullary hypotonicity (wash-out) in the aged. These changes with ageing are accompanied by a decrease in the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF). However, because ERPF decreases proportionally more than GFR – 10% per decade from 600 ml min^{-1} 1.73 m^{-2} in youth to 300 ml min^{-1} 1.73 m^{-2} by the age of 80 years, the filtration fraction (FF), which is the ratio of GFR/ERPF, usually increases in the elderly because the denominator (EFRF) is disproportionately lower than the numerator (GFR).[2–4]

Measurement of the GFR with ^{51}Cr EDTA confirms that the healthy elderly have a lower GFR than the young. At the third decade of life, GFR peaks at approximately 140 ml min^{-1} 1.73 m^{-2}, and from then on, GFR progressively declines at an approximate rate of 8 ml min^{-1} 1.73 m^{-2} per decade. A similar fall in creatinine clearance (Ccr) is accompanied by a concomitant decrease in creatinine production (senile sarcopenia), and consequently serum creatinine does not increase with the progressive decrease in GFR.[5]

However, in approximately one third of old people the GFR does not decrease with age. Since Kimmel *et al*. have demonstrated that old people who were on a high protein diet maintained a normal GFR, it has been hypothesized that 'normal' GFR in the elderly could be the consequence of increased protein intake that is followed by glomerular hyperfiltration.[5]

In clinical practice, Ccr is estimated using the Cockcroft and Gault equation: Ccr = (140-age) × (body weight)/72 × serum creatinine (15% lower in women).[6] Another frequently used equation is the MDRD (modification of diet in renal disease) formula: GFR = 186 × serum creatinine$^{-1.154}$ × age (in years) $^{-0.203}$ × (0.742 if female) × (1.210 if black race). When applied to the elderly each of these formulas has its advantages and disadvantages. Thus, the Cockcroft-Gault formula underestimates GFR in people >80 years, while the MDRD equation has the advantage of not requiring the patient's weight for calculating GFR. There is a poor correlation between GFR obtained by MDRD formula and the measured creatinine clearance with cimetidine, which is a proxy of the GFR gold standard measured by inulin clearance; conversely this study showed a good correlation between the Ccr obtained by Cockcroft-Gault (CG) formula and that measured by creatinine clearance with cimetidine.[6] Keller believes that the easiest formula for estimating GFR in people between

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25 and 100 years old is as follows: GFR = 130-age (in years) ml min^{-1}, but this has not been validated by direct comparison with creatinine clearance with cimetidine.[5–8]

Regarding cystatin-C as a GRF marker, it has been demonstrated that in elderly persons with glomerular filtration lower than 60 ml min^{-1}, it is not superior to that calculated by the CG and MDRD formulae.[5,9]

Consequences of senile hypofiltration

- A serum creatinine concentration of 1 mg dl^{-1} reflects a GFR of 120 ml min^{-1} in a 20-year-old and 60 ml min^{-1} in an 80-year-old.[5,9]
- Senile hypofiltration and diastolic cardiac failure predispose healthy old people to cardiac failure, and to lung congestion after a saline load.[9]
- The dose of prescribed drugs must be adjusted to the estimated GFR in the elderly.[8]
- In old people senile hypofiltration differs from chronic kidney disease because the glomerular filtration value is stable over a period of 6–12 months and there is no haematuria or significant proteinuria (>0.30 g day^{-1}).[10]

Diseases: At the glomerular level

Glomerulonephritis

Renal biopsy is useful in guiding the prognosis and therapy for renal disorders in this population. In the elderly who underwent a diagnostic renal biopsy, 59% had primary glomerulonephritis, and 20% secondary glomerulonephritis. Even though the aged accounted for only 23% of patients undergoing biopsy, the elderly in the biopsy series were more numerous than the proportion of elderly people in the general population (16%). Primary glomerulonephritis was the most frequent biopsy-proven renal disease in the elderly, even more frequent than primary glomerulonephritis in adults. Although the indications and incidence of complications of renal biopsy are the same for both elderly and adults, when older persons have a complication of renal biopsy, generally such complications are more serious. Crescentic, membranous nephropathy, membranoproliferative glomerulonephritis, minimal change disease, and acute post-streptococcal glomerulonephritis are all more frequent in the elderly than in younger patients. Only focal segmental glomerulosclerosis, IgA and non-IgA mesangioproliferative nephritis were less frequent in elderly patients than in the younger ones.[11–13]

In some elderly patients membranous nephropathy is related to drugs ingestion or an underlying malignancy (20%) (mainly lung or colon adenocarcinoma). Regarding minimal change disease, senile structural renal changes make histological diagnosis difficult; its clinical presentation is usually 'atypical' with hypertension, microhaematuria and/or renal failure; also it may be associated with drugs (NSAIDs) or malignancies (lymphoma). Crescentic glomerulonephritis reaches its greatest incidence between 60–79 years of age, and its typical clinical presentation is an acute renal failure of rapid evolution. Steroids and other immunosuppressive drugs (cyclophosphamide, etc.) can be used in the elderly as in adults, though with special attention to their side effects. Secondary glomerulopathies such as diabetic nephropathy, nephroangiosclerosis secondary to essential hypertension, glomerular vasculitis, and those associated with abnormal plasma-cell proteins (light chain, fibrillary, immunotactoid nephropathy) are frequent in the elderly. Nephrotic syndrome accounts for 50% of renal biopsy indications, its most prevalent causes are: membranous, minimal change, diabetic and amyloidosis nephropathies.[12–14]

Normal ageing: Renovascular level

Senile renal vascular changes

Prearterioles show subendothelial deposition of hyaline and collagen fibres that produce intimal thickening. In the small arteries the intima is thickened due to proliferation of the elastic tissue, and the media shows atrophy. Another characteristic of the ageing kidney is the formation of the above-mentioned *aglomerular circulation*, and dysfunction of the autonomic vascular reflex.[2,3,10,14]

Consequences of the senile vascular changes

- Renovascular atherosclerosis, which can lead to renovascular hypertension, ischaemic nephropathy and chronic kidney disease.[9,14]
- In patients with bilateral renal artery stenosis reversible renal failure may develop after the use of angiotensin-converting enzyme (ACE) inhibitors.[14,15]
- Intrarenal atheroembolism appears when plaque material breaks free from the diseased renal artery and enters the renal circulation. The kidney rarely recovers from this acute insult.[14]
- Renal dysautonomia leads to kidney damage during hypotensive or hypertensive states.[9]

Diseases: Reno-vascular level

Renal vasculitis in the elderly

It has become increasingly clear that renal vasculitis is more common with advancing age and probably this disease is the most common primary cause of renal failure in the elderly. The incidence of Wegener's granulomatosis and microscopic polyangeitis increases with age. Since immunosuppression is the main treatment for these entities, a careful monitoring of therapy can minimize adverse effects in this population.[13,14]

Other diseases: renovascular atherosclerosis and atheroembolic disease.

Normal ageing: Tubular-interstitial level

Senile tubular-interstitial changes

Renal tubules undergo fatty degeneration, and irregular thickening of their basal membrane. Diverticula arise from the distal and convoluted tubules, and it has been suggested that, in the aged, these may serve as reservoirs for recurrent urinary tract infections in the elderly. In addition, the aged kidney also shows increasing zones of tubular atrophy and fibrosis.[2,3]

Consequences of tubular-interstitial changes

The physiological and clinical consequences of these changes in the aged renal tubules can be summarized in three groups: (1) tubular dysfunction, (2) medullary hypotonicity, and (3) tubular frailty.

1 ***Tubular dysfunction:*** Compared to younger individuals tubular handling of many substances is modified in healthy elderly people: [9]

- **Sodium** The 24-hour urinary sodium output and fractional excretion of sodium are significantly greater in old and very old people. The mean half time for the excretion of a sodium load is 17.7 hours in persons under 30 years of age, reaching 30.9 hours in persons over 65. Because GFR declines with age and the amount of filtered sodium is lower than in young subjects, a salt load given to an aged person takes longer to eliminate. However, when sodium is restricted to 50 mmol day^{-1}, the period required to start saving urinary sodium is five days in the young and nine days in the elderly, and therefore the capacity of the ageing kidney to adapt to a low salt intake (50 mmol $24h^{-1}$) is clearly blunted. The proximal nephron behaves similarly in the young, old and very old, whereas in the thick ascending loop of Henle the reabsorption of sodium is reduced in the old and very old people. This phenomenon has two important consequences: first, the amount of sodium loss is increased; and second, the capacity of the medullar interstitium to concentrate is also diminished (medullary hypotonicity). Thus, old subjects exhibit both an increased sodium excretion and an inability to maximally concentrate the urine (water saving). Despite this tendency to an exaggerated natriuresis, total body sodium is not significantly decreased with age. The basal plasma concentrations of renin and aldosterone and the response to their stimuli are diminished in old age, which is another mechanism for the enhanced sodium loss in this population. Finally, elevated serum and urinary natriuretic peptide levels in the elderly may be another cause of the characteristic urinary sodium loss of the aged.[4,16,17]

  Clinical consequences: For therapeutic reasons or due to reduced appetite, salt-restricted elderly can develop hyponatraemia (senile 'sodium leakage' hyponatraemia), volume depletion (hypotension, hypernatraemia) and even acute renal failure (ARF).[4,16,17]

- **Potassium** Total body potassium content is lower in the old than in the young, and the correlation with age is linear. This phenomenon can be explained by the reduced muscle mass (main body potassium stores), and poor potassium intake characteristic of the elderly. On the other hand, the renal excretion of potassium is significantly lower in the aged. A trend to hyperkalaemia in the elderly is explained by the reduced serum aldosterone and reduced tubular response to this hormone. In addition, there is an increase in the activity of the H+K+ATPase pump (potassium reabsorption) in the intercalated cells of the aged collecting ducts (in rats). This mechanism could also explain the trend to hyperkalaemia in old people.[18–20]

  Clinical consequences: Usually serum potassium is normal in the elderly, but when they take diuretics, they develop hypokalaemia more rapidly than do the young. On the other hand elderly persons are predisposed to hyperkalaemia, particularly when they are treated with non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, beta-blockers and/or potassium-sparing diuretics.[18–20]

- **Urea, creatinine and uric acid** In healthy old and very old people, fractional excretion of urea is increased compared to that in younger persons: 65% and 50% respectively. This phenomenon could be explained by a reduced distal urea reabsorption secondary to the diminished UT1 (urea channels) demonstrated in the collecting tubules in old rats. Regarding the handling of creatinine, it has been shown that healthy older people have a net creatinine tubular reabsorption. Serum uric acid levels and its urinary fractional excretion are similar in the young and the old.[6,21]

  Clinical consequences: The increased urinary loss of urea contributes to osmotic diuresis (nocturia), and medullary hypotonicity that can lead to dehydration in hot weather, febrile syndromes, as well as a characteristic low serum urea level in healthy old. Also creatinine clearance can lead to underestimation of glomerular filtration in the healthy old individuals because this group shows net creatinine reabsorption.[6,21,22]

- **Calcium, phosphate and magnesium** Serum calcium, phosphorus and magnesium levels and their urinary fractional excretion are similar in the healthy young, old and very old. However, since the elderly frequently have a low vitamin D diet, reduced sunlight exposure, decreased vitamin D renal hydroxylation and a low level of serum sexual hormones, they tend to develop calcium metabolism disorders. The latter phenomenon in combination with a poor calcium intestinal absorption leads to the development of senile secondary hyperparathyroidism. When healthy old people undergo a volume

overload, renal magnesium excretion is increased to a degree that significantly lowers their serum Mg level. Since, in healthy old people, sodium reabsorption is reduced in the thick ascending loop of Henle and magnesium reabsorption occurs chiefly at this tubular segment, one could hypothesize that a urinary magnesium loss could explain the increased Mg excretion. In addition, it is known that the elderly often need magnesium supplements probably because of a combination of diminished spontaneous intake of magnesium and poor intestinal absorption.[22]

Clinical consequences: Even though renal handling of calcium, phosphate and magnesium are not altered in the elderly, their lower ingestion and intestinal absorption can easily lead to hypocalcaemia, hypomagnesaemia, hypophosphatemia, and secondary hyperparathyroidism. [22]

- **Urinary acidification** Macias *et al*. found no differences in titratable acid, ammonia or net acid excretion in response to an acute acid overload in the elderly compared to young controls. However, following an acid load, the maximal values of ammonia and titratable acid excretion were reached in four hours in the young and between six and eight hours in the old.

Clinical consequences: elderly subjects take longer to reach peak proton (acid) excretion, and experience a greater difficulty in handling states of acidosis. [22]

- **Erythropoietin** Erythropoietin is mainly produced by the peri-tubular interstitial cells near the proximal convoluted tubules. Erythropoietin production is not affected by age and therefore its plasma levels are normal in the healthy old and very old people.

Clinical consequences: Normal ageing process does not explain the presence of anaemia.[23]

2 ***Medulla hypotonicity: water handling:*** Total body water is diminished with age; in the elderly it comprises only 54% of total body weight compared to 65% in the young. As in healthy young people, total body water content is lower in elderly women, than in elderly men. Since the reduction in senile water content takes place in the intracellular compartment, hypovolaemia always represents a pathological state in the elderly. Senescence reduces the capacity of the kidney to concentrate the urine. The maximum urinary concentration capacity remains normal until about the third decade and then it falls by about 30 mOsmol kg^{-1} per decade. This phenomenon can be explained by the *aglomerular circulation*, the defect in sodium reabsorption in the ascending limb of Henle's loop, and the reduced distal urea reabsorption, which in the young kidney induces the development of a hypertonic medulla. Another mechanism for the impairment of the urine concentration ability is the decrease in responsiveness of tubular epithelium of the collecting tubules to antidiuretic hormone. Also this may explain why plasma vasopressin levels are higher in the elderly compared to mature adults. Furthermore, when healthy active elderly volunteers were water-restricted for 24 hours, their threshold for thirst was increased and water intake was reduced compared with a control group of younger subjects. Dryness of the mouth, a decrease of taste, alteration in mental capacity or cortical cerebral dysfunction, and a reduction in the sensitivity of both osmoreceptors and baroreceptors all may contribute to this increased threshold for thirst. Finally, concentration of angiotensin, a powerful generator of thirst, is lower in the elderly. Urinary dilution capability is also decreased. Thus, there is a minimum urine concentration of only 92 mOsmol kg^{-1} in the elderly compared to 52 mOsmol kg^{-1} in the young. Maximum free water clearance also is reduced in the elderly from 16.2 ml min^{-1} to 5.9 ml min^{-1}. Again, the functional impairment of the diluting segment of the thick ascending limb, described above, seems to account for the decrease in the capacity to dilute urine observed in the aged.[4,9,24]

Clinical consequences: Elderly people may develop dehydration (hypernatremia) or volume overload (hyponatremia) under conditions of water restriction or water load respectively.

3 ***Tubular frailty:***Tubular cells are frail in the elderly, and because of this they progress easily to acute tubular necrosis, and also they recover slowly from this histological alteration.[9]

Clinical consequences: Acute kidney injury (AKI) is a frequent complication in the elderly, and if the kidney does not recover after approximately three months it remains as *chronic kidney disease* (CKD).[9]

Diseases: Tubular-interstitial level

Interstitial nephritis

Although acute interstitial nephritis may develop following the use of nearly all NSAIDs or diuretics the number of reported cases is small. Most of these patients are elderly. Usually the associated renal abnormalities improve after the drug is discontinued with or without steroid therapy, but possible complications may include chronic kidney disease or even end-stage renal disease (ESRD). Interstitial nephritis results mainly from a delayed hypersensitivity response to drugs (NSAID, diuretics, etc.). Patients taking NSAIDs for months or years may develop papillary necrosis, chronic interstitial nephritis, or even ESRD.[14]

Urinary tract infection (pyelonephritis)

This is the most common infection in the elderly and is especially frequent in debilitated, institutionalized individuals. Its pathogenesis is strongly related to obstructive uropathy. Moreover, the incidence of bacteriuria increases with advancing age because of several non-obstructive

conditions such as vaginal and urethral atrophy, puddling related to bed rest, and bladder catheterization which predispose the aged to urinary infection.[25]

Obstructive uropathy

Prostatic hypertrophy occurs to the same degree in almost all ageing males, but in a proportion of them it provides a slow obstruction to urinary outflow, which gradually decreases kidney function. Often this is not recognized until it is too late, largely because the patient becomes polyuric rather than oliguric. By the time, the urinary obstruction is recognized, the damage may be irreversible, so that even with the relief of obstruction, renal function recovers only partially.[9,26]

Acute kidney injury (AKI)

The most common causes of AKI in the elderly are:

1 Prerenal causes: dehydration (main cause), haemorrhage and shock (cardiogenic and septic).

2 Renal causes: acute tubular necrosis (ATN) due to the persistence of prerenal causes and/or to nephrotoxins (e.g. aminoglycosides), rapidly progressive damage due to primary or secondary glomerular disease, or acute interstitial nephritis.

3 Postrenal (obstructive) causes: stones, tumour, stricture, prostatic hypertrophy.

Prerenal and postrenal causes of AKI are of particular importance because their early identification and treatment may prevent the development or reverse established AKI. The cause of AKI is often multifactorial and its incidence is higher in the elderly than in the young, because of the frequency of systemic illnesses (diabetes mellitus, myeloma, etc.), polypharmacy, and because of the renal ageing process itself. However, age *per se* is not an important determinant of survival in patients with AKI. In the elderly, the urinary indices (urinary sodium and fractional excretion of sodium and urea) for diagnosing AKI may be slightly different from those accepted for younger people since a higher value of these indicators does not rule out a prerenal AKI (due to the senile urinary sodium and urea loss). Sometimes temporary or permanent dialysis may be needed.

Although AKI is treated similarly in the elderly and younger patients, old people are more vulnerable to dialysis-related complications such as haemodynamic instability, bleeding and mild disequilibrium syndrome.

Prevention is of paramount importance: maintenance of an adequate extracellular volume and drug dosage regimens tailored to the patient's GFR are essential.[15]

Chronic kidney disease (CKD)

CKD is a syndrome characterized by progressive and generally irreversible deterioration of renal function due to the reduction of the nephron mass. CKD is predominantly a disease of the elderly, because its incidence rises steadily with age, being at least 10 times more common at 75 and over than at 15–45 years. The causes of end-stage renal disease (ESRD) in the elderly differ substantially from those in younger populations. The most common disorders that lead to renal failure in old age are hypertension, nephrosclerosis, diabetes mellitus and obstructive uropathy, although in as many as one third it proves impossible to identify any specific cause. Two common causes of CKD are: vascular disease of the main renal arteries and prostatic hypertrophy. A further cause worth noting is amyloidosis. Pathogenic mechanisms by which the failing kidney may produce specific clinical features are as follows:

- As sclerosis of the glomeruli advances, the remaining nephrons shift to glomerular hyperfiltration in order to eliminate more waste toxic products per functioning nephron (hyperfiltration). This mechanism appears beneficial at the beginning but the price paid for hyperfiltration is an acceleration of glomerular sclerosis;
- Retention of uremic toxins (polyamines, guanidines, middle molecules and hormonal peptides);
- A high level of parathyroid hormone is currently accepted as one of the major uremic toxins;
- Erythropoietin and 1,25-dihydroxycholecalciferol deficiencies result in anaemia and low serum calcium, respectively;
- Phosphate retention leads to secondary hyperparathyroidism and renal osteodystrophy;
- Derangement of the renin angiotensin aldosterone mechanism results in hypertension. As CKD progresses and creatinine clearance falls to about 25 ml min^{-1}, the full clinical picture of uremia appears. The skin acquires a characteristic yellow-brown pallor and pruritus is frequent. Patients complain of asthenia, anorexia and vomiting. From the cardiorespiratory system, hypertension, heart failure, pulmonary oedema, coronary disease and arrhythmia may be seen. From the nervous system the patient may have polyneuropathy, clonus and even uremic coma in the most advanced stage of the disease. Secondary hyperparathyroidism, and hyperprolactinaemia are frequent endocrinological abnormalities. Impaired cellular immunity, and clotting alterations are also present. In the late phase, all of the above abnormalities increase and, when GFR is lower than 10 ml min^{-1}, it is necessary to start replacement therapy (dialysis or transplantation).[7,10]

Dialysis: Age itself does not constitute a contraindication to dialysis and/or transplantation. Elderly patients can be effectively treated by both haemodialysis (HD) or peritoneal dialysis (PD). Old patients on dialysis are prone to develop more serious forms of bone disease than the

young, due to osteopenia, unbalanced diet, reduced physical activity and lack of exposure to sunlight. Frequently malnutrition is present and in order to prevent this state, it is advisable to provide more than 1 g kg^{-1} body weight of protein for patients on HD, and more than 1.2 g for those on PD. The most common practical problems during HD in aged patients are: difficulty in creation of the arteriovenous fistula, permanent catheter/graft infection, gastrointestinal bleeding, intradialytic hypotension, headaches, vomiting, cramps, angina, arrhythmias and cardiovascular instability, while in elderly patients on PD most practical problems are: dialysate leakage, formation of hernias, backache, difficulty in learning, social isolation, family burn-out, and worsening of peripheral vascular disease or malnutrition. PD is better for patients with residual diuresis, severe hypotension, complicated and/or short-lived vascular access, intradialytic arrhythmias, angina or cardiovascular instability. Besides, PD is a satisfactory alternative for geriatric ESRD patients. Most studies confirm that elderly patients on PD and HD have similar survivals. Other forms of peritoneal dialysis include various forms of automated peritoneal dialysis (APD) such as continuous cycling peritoneal dialysis (CCPD) and nightly peritoneal dialysis (NPD); the latter can be an alternative treatment for more vulnerable elderly patients (nursing home).

The predictors of poor outcomes in elderly on dialysis are poor nutritional status, dementia, gait disorders, altered activities of daily living (ADL) and instrumental activities of daily living (IADL), and late referral to the nephrology service. Very elderly patients on haemodialysis have a poor life expectancy: median survival time is 15.6 months from 80–84 years of age, and 11.6 months for those 85–89 (USA). The main causes of death in the oldest dialysis patients are elective withdrawal (38%), cardiovascular events (24%) and infection (22%).[27–29]

Transplantation: Success of transplantation in geriatric ESRD patients requires improved patient selection, the use of new immunosuppressive drugs and lower doses of corticosteroids. One can achieve one-year patient and graft survival rates of 85% and 75%, respectively. For patients older than 60–65 years, the five-year 'functional' graft survival is 55–60%. Although overall results are excellent, the management of transplantation in the elderly requires an understanding of pharmacology, immunology and physiology peculiar to this age group. Although these patients experience fewer rejection episodes than do younger patients, graft loss in the elderly transplant recipient is due mainly to death with a functioning graft.[30]

In addition, transplant stress induces senescence changes in the kidney, while the greatest adverse impact factor in cadaver kidney transplant today is donor age. Most common causes of death in the elderly transplant recipient are cardiovascular disease and infection related to peaks of immunosuppression. Regarding the elderly people as kidney donors, their organs are considered as marginal ones, but these can be useful (single or in pair) in a subgroup of elderly recipients.[30]

Renal pharmacology

Many pharmacokinetic parameters are affected by the ageing process such as: the amount of drug that reaches the systemic circulation and therefore the amount at the site of action (bioavailability), the distribution size of the drug (volume of distribution), its renal excretion (GFR), and the length of time needed to reach steady-state serum concentration or to eliminate the drug (four times the halflife). Due to these pharmacokinetic changes, old people are predisposed to drug toxicity, and treatment should be individualized, using low and slowly increasing doses, and trying to avoid polypharmacy.[8]

Key points

- Numerous physiological changes occur in the kidney during ageing.
- Elderly patients can be effectively treated with either haemodialysis or peritoneal dialysis.
- For persons >60 years of age five-year survival of a renal transplantation graft is 55–60%.

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SECTION 12

Cancer

CHAPTER 108

Cancer and ageing

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Introduction

The risk of most types of cancer increases with age and with the growth in the aged segment of the population, the burden of cancer in the elderly will continue to grow. In this chapter, the scope of this problem is reviewed, as is the biology of cancer and ageing. A discussion on cancer prevention and treatment in the elderly follows. Finally, supportive care, survivorship issues and the multidisciplinary care of the senior adult cancer patient are reviewed.

Epidemiology and disparities

Cancer is the leading cause of death in men and women aged 60–79 years and the second leading cause of death in persons aged 80 years and older.[1] By 2030, more than one-fifth of the population in the USA will be over the age of 65 years.[2] The probability of developing cancer is one in three in men and one in four women over the age 70 years. The leading causes of cancer incidence and mortality are detailed in Figure 108.1.

Over the past 60 years, cancer-specific death rates have decreased among younger individuals, while increasing in older individuals.[3] Significant disparities in outcomes between younger and older individuals are likely due to a number of factors, including differences in screening, more advanced stage at presentation in older individuals or less aggressive treatment in older patients. Older individuals are more likely to experience delays in diagnosis, incomplete evaluation and undertreatment. Half of older women receive substandard treatment for breast cancer, with significantly worse survival.[4] Similar trends have also been noted among patients with ovarian and rectal cancer and these persist even when studies control for comorbidities and functional status. Under-enrolment of older individuals in clinical trials further compounds the situation by resulting in a paucity of data on appropriate management of cancer in the elderly.

Ageing and tumour development

Hanahan and Weinberg proposed that there are six attributes that must be attained by a cell to be transformed into a malignant cell: self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis and tissue invasion/metastasis.[5] Mutations cause cellular changes resulting in these altered characteristics and in malignant transformation.

Theories of biological ageing and carcinogenesis overlap in many ways, potentially explaining the increased incidence of many cancers with age. Over time, DNA damage caused by random events or free radicals can cause either cellular dysfunction/death, resulting in ageing, or may cause mutations in proto-oncogenes or tumour suppressors, yielding carcinogenesis. Further, changes seen in cells with ageing are also observed in early carcinogenesis. The formation of DNA adducts, DNA hypomethylation, chromosomal breakage and translocation are associated with age and increase the susceptibility to late-stage carcinogens.[6]

The immune dysregulation associated with ageing may contribute to the increased incidence of cancer with age. With age, changes in T-cell function result in decreased proliferation, increased proportion of memory cells and a decrease in naive T-cells. B-cell function is intact but dysregulated, with an increase in autoantibody formation and monoclonal protein production. Interleukin-2 levels decrease, whereas interleukin-6 levels rise. A prospective cohort study demonstrated that individuals with better NK cell function had lower rates of cancer 10 years subsequently.[6]

In some ways, however, ageing and cancer biology are at odds: cancer requires limitless replicative potential, while finite replicative potential (replicative senescence) is a hallmark of ageing. Most normal human cell types have the capacity for 60–70 doublings. The cellular 'abacus' is the telomere, which consists of several thousand repeats of a

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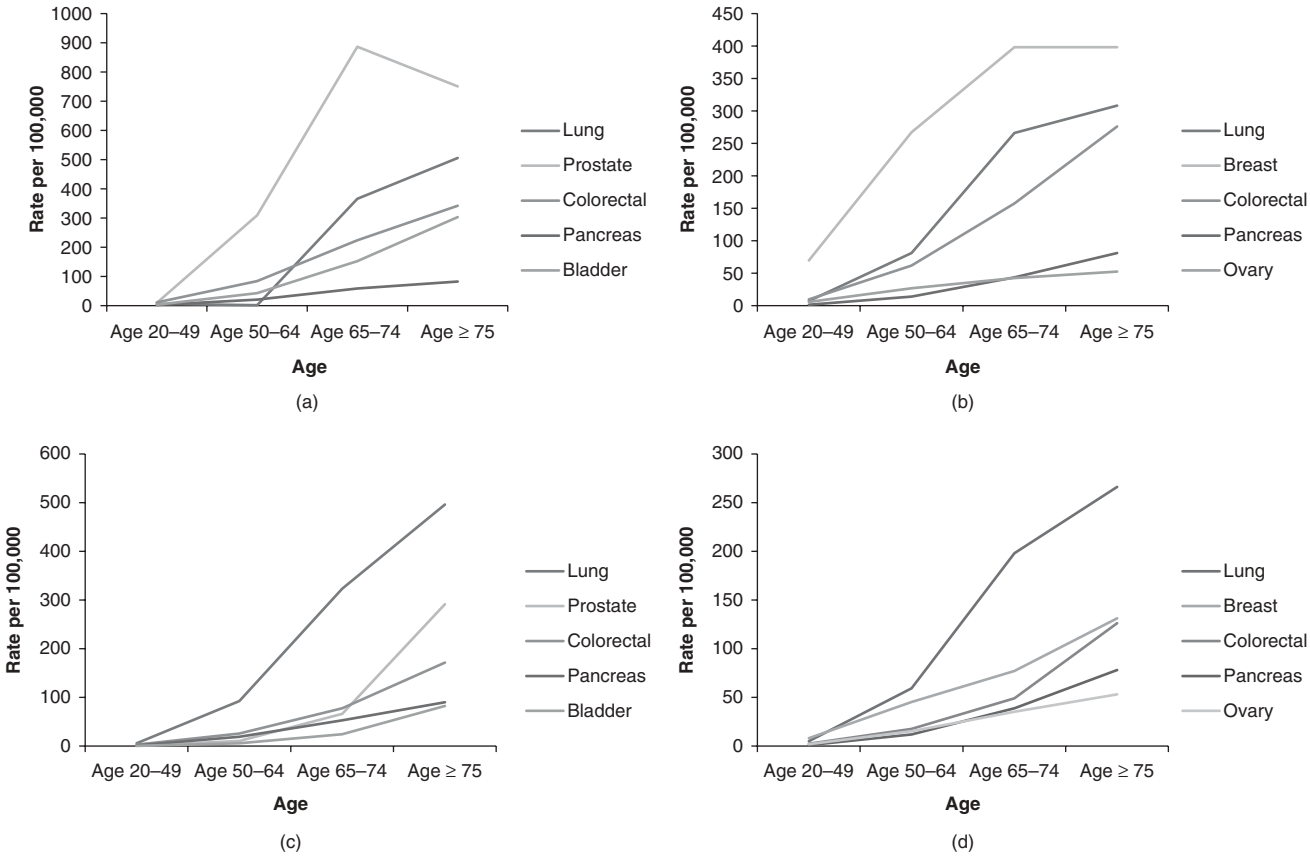

Figure 108.1 (a) Cancer incidence rates in men; (b) cancer incidence rates in women; (c) cancer mortality rates in men; (d) cancer mortality rates in women. All rates age adjusted to 2000 US population. 2006 SEER statistics.

short base pair sequence at the ends of every chromosome. The telomeres protect the chromosomal DNA. With each successive replication, 50–100 base pairs of telomeric DNA are lost from the ends of the chromosomes. Over time, in normal cells, these protective caps are lost; the chromosomal DNA becomes fused end-to-end with other chromosomes, ultimately leading to death of the affected cell. In contrast, in malignant cells, telomeres are maintained through the expression of telomerase, allowing unlimited replication.[7] Another mechanism of senescence, termed 'stress-induced premature senescence', results from cellular events other than telomere shortening. Mutations in an oncogene or double-stranded DNA breaks induced by chemotherapeutic agents can trigger senescence, resulting in a proportion of clonal cells entering senescence. This permanent growth arrest may be as effective as apoptosis as an anti-cancer mechanism.[8]

In some malignancies, there are age-related differences in tumour biology, making the malignancy either more or less aggressive in older patients compared with their younger counterparts. It is a commonly held, though debatable, dogma that solid tumours, including breast, colon, lung and prostate cancer, are more indolent in older patients; however, epidemiological data do not altogether support this observation. It is clear that in some cancers, there are differences in tumour behaviour over the age spectrum. Breast cancers in older women are more likely to be estrogen receptor positive. Acute myeloid leukaemia is more aggressive in elderly patients and more resistant to conventional chemotherapy due to the increased expression of the MDR1 (multidrug resistance) gene.

Cancer prevention

Cancer prevention is an effective way to reduce cancer morbidity and mortality. Cancer prevention strategies include behavioural/lifestyle modification, such as dietary changes, chemoprevention and screening.

Obesity is associated with post-menopausal breast cancer and weight loss lowers circulating estrogen levels. Large cohort studies demonstrate that weight loss is associated with a decreased risk of post-menopausal breast cancer.[9] Further, a randomized trial of a lower fat dietary intervention, which resulted in weight loss in the intervention group, was associated with an 11% reduction (hazard ratio 0.89, 95% confidence interval 0.80–1.00) in estrogen receptor

positive (ER+) post-menopausal breast cancer diagnoses in the 8 years of follow-up.[10] Further research is needed into whether it is weight loss *per se* or dietary modification that results in the reduced risk of cancer. In this same trial, however, there was no change in the incidence of colorectal cancer with the dietary intervention.[11]

Epidemiological studies suggest a protective effect of increased calcium and vitamin D intake on the risk of colorectal cancer. Randomized trials have demonstrated a modest but significant decrease in risk of recurrent adenomas. In the Women's Health Initiative randomized trial, supplementation with calcium and vitamin D did not result in a decrease in the risk of colorectal cancer versus placebo.[12] However, this study was criticized for doses of vitamin D_3 (400 IU daily) that are generally inadequate to achieve sufficient serum levels of 25-hydroxyvitamin D.

The inducible enzyme cyclooxygenase 2 (COX-2) is elevated in the majority of colorectal cancers. Aspirin, a non-specific inhibitor of both COX-1 and COX-2, reduces the risk of colorectal cancer by 24% in patients who take at least 300 mg of the medication for at least 5 years and after a latency period of 10 years.[13] However, the benefit of cancer prevention must be weighed against the risk of bleeding complications. The COX-2 inhibitor's more selective mechanism results in lower risk of bleeding. Indeed, the COX-2 inhibitors rofecoxib and celecoxib effectively prevent the formation of precancerous polyps, but are also associated with an increased risk of cardiovascular events.[14] Given the increased risk and no data showing a decreased risk of invasive colorectal cancer, COX-2 inhibitors should not yet be used for colorectal cancer prevention.

The selective estrogen receptor modulators (SERMs) compete with estrogen for binding at the estrogen receptor, inhibiting pathways required for cellular growth and proliferation. A randomized, placebo-controlled trial of tamoxifen for the prevention of breast cancer enrolled over 13 000 women. Tamoxifen reduced the risk of invasive breast cancer by more than 40%. Therapy with tamoxifen was associated with a twofold increased risk of pulmonary embolism and a threefold increased risk of endometrial cancer.[15] Given the serious potential side effects, tamoxifen is recommended only for women at high risk for cancer using risk prediction models such as the Gail model, weighed against the individual risk factors for adverse events.[16]

Another SERM, raloxifene, has been studied with regard to its impact on the incidence of post-menopausal breast cancer. Over the 8 years of follow-up, therapy with raloxifene was associated with a 76% reduction in the incidence of ER+ breast cancers, relative to placebo. Women treated with raloxifene had a twofold increased risk of venous thromboembolic disease.[17] In a head-to-head comparison, postmenopausal women at increased risk for breast cancer were randomized to either raloxifene or tamoxifen. Raloxifene was as effective as tamoxifen at reducing the risk of invasive breast cancer, with a lower risk of venous thromboembolic events.[18]

In summary, several cancer prevention strategies hold promise. However, in an individual patient, the risks and benefits must be considered before recommending chemopreventive strategies.

Cancer screening

Screening as a strategy for prevention is a complicated issue. The goal of screening is to identify a disease during a latent or early symptomatic stage, in order to intervene and alter the natural history of disease. Although there is evidence of benefit of screening for breast, colorectal and cervical cancer in individuals in their 50s and 60s, data for screening older, asymptomatic individuals for these common malignancies is lacking. Complicating the issue are the differences in cancer biology described above, which may result in the detection of more indolent cancers that would not ultimately be life-limiting. The sensitivity and specificity of screening tests may be affected by age-related changes in body composition, such as the change in breast composition with age. The harm due to false-positive screening tests must also be taken into account, including psychological distress and risks of diagnostic procedures. Comorbid medical conditions and functional decline may increase the risk of complications related to screening procedures, such as the sedation required for colonoscopy. Table 108.1 gives a summary of current recommendations regarding screening.

Colorectal cancer screening is effective in selected older patients. In patients aged 70–80 years, randomized trials have shown annual to biennial faecal occult blood testing (FOBT) to be effective at reducing colorectal cancer incidence and mortality, with a lag time of 5 years to mortality benefit. However, the sensitivity and specificity are low. Case–control studies of flexible sigmoidoscopy and colonoscopy in older patients suggest a mortality benefit associated with screening; however, sigmoidoscopy has a lower sensitivity in older individuals given the increase in prevalence of right-sided colon cancers, which sigmoidoscopy does not detect. Colonoscopy is more sensitive and specific than FOBT or sigmoidoscopy, but in a cohort of older patients aged 70–75 years, the rate of major complications of colonoscopy, including perforation, myocardial infarction or stroke, was 0.3%.[19] Computed tomographic (CT) colonography appears to be as effective as colonoscopy in older patients at detecting advanced neoplasias, with a low false-positive rate,[20] but must be followed by traditional colonoscopy to confirm abnormal findings.

Among the randomized trials that established the mortality benefit of mammographic screening for breast

Table 108.1 Recommendations for cancer screening in older adults[a].

Cancer	USPSTF[55]	ACS[56]	AGS
Colorectal cancer	Age 50–75 years: FOBT, sigmoidoscopy or colonoscopy recommended Age 76–85 years: recommends against routine screening, although there may be considerations supporting screening in an individual Age >85 years: recommends against screening	Starting at age 50 years and continuing as long as individual is in good health	Age ≥50 years: screening recommended, unless person is too frail to undergo colonoscopy or life expectancy <5 years[57]
Breast cancer	Age 50–74 years: biennial mammography Age ≥75 years: insufficient evidence to assess risks and benefits of screening mammography	Beginning at age 40 years and continuing as long as the woman is in good health and would be a candidate for breast cancer treatment	Age <75 years: annual or biennial mammography Age ≥75 years: mammography at least every 3 years with no upper age limit for women with an estimated life expectancy of ≥4 years[58]
Cervical cancer	Cessation of screening for women >65 years with adequate prior screening who are not otherwise at high risk for cervical cancer	Cessation of screening for women ≥70 years with ≥3 recent, consecutive negative tests and no abnormal tests in previous 10 years	Age ≤70 years: screening every 1–3 years Age >70 years: little evidence for or against screening women who have been regularly screened in previous years. An older woman of any age should who has never had a pap smear should be screened until two negative pap smears taken 1 year apart[59]
Prostate cancer	Age <75 years: current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening Age ≥75 years: recommends against screening for prostate cancer	Healthcare provider should discuss risks and benefits of screening with the men at average risk for prostate cancer and with 10 year life expectancy, beginning at age 50 years	No published recommendations

[a]USPSTF, U.S. Preventative Services Task Force: ACS, American Cancer Society; AGS, American Geriatric Society: FOBT, faecal occult blood testing.

cancer, only one included women over the age of 70 years. Although in the overall study mammography decreased the risk of breast cancer death by one-third, there was not a significant reduction in breast cancer mortality in the subgroup of women aged 70–74 years. Interestingly, as the density of breast tissue decreases with age, the sensitivity and specificity of mammography increase. There are several studies demonstrating that among women with multiple comorbidities, detecting early-stage breast cancer does not improve survival. Thus, women with a life expectancy of less than 5 years are unlikely to benefit from breast cancer screening.[19]

There have been no prospective randomized trials of cervical cancer screening in any age group, although multiple observational studies show that screening with Papanicolaou (Pap) smears decreases the incidence and mortality of cervical cancer. With advancing age, the sensitivity of Pap smears decreases due to the migration of the squamo-columnar junction into the cervical canal and specificity declines due to atropic changes causing inflammation. Older women who have been regularly screened are at low risk and those who have significant comorbidity are unlikely to benefit from screening.[19]

Prostate cancer screening is controversial, even in younger populations. Prospective, randomized trials of prostate-specific antigen (PSA) screening are under way, but do not include men over the age of 75 years. Given the indolent nature of most prostate cancers and high prevalence of clinically irrelevant prostate cancers found among octogenarians at autopsy, screening for prostate cancer

is generally not recommended in men over the age of 75 years or who have a life expectancy of less than 10 years.[21]

In summary, selected older individuals with longer life expectancy may be appropriate for screening for common cancers.

Cancer treatment

The basic tenets of cancer treatment involve the determination of whether treatment is being undertaken with curative or palliative intent. Radiation therapy and surgery are the modalities of treatment utilized to control the local extent of cancer. Cytotoxic chemotherapy, hormonal therapy, biological therapy or targeted agents are typically administered orally or intravenously for systemic treatment. Treatment may be administered neoadjuvantly, that is, prior to definitive treatment, to limit the chance of systemic spread and to decrease the extent of local treatment. Adjuvant therapy is administered following definitive treatment, to reduce the risk of recurrence in individuals at high risk. Palliative treatment is administered to improve symptoms or prolong life in patients with an incurable malignancy.

Decision-making

Historically, clinical trials of cancer treatment have excluded patients due to advancing age or therapies in older patients. Clinicians have been left to extrapolate from data derived from the treatment of younger individuals. Increasing attention to this problem has yielded both retrospective and prospective studies of the effectiveness of treatment strategies in older adults with cancer, but much work remains to be done. Guidelines for the approach to management of cancer in senior adults have been established (Figure 108.2).

Surgery

Surgery is employed in the treatment of cancer to remove the primary tumour with curative intent. Surgery may also be used to palliate symptoms or prevent serious complications in advanced or metastatic disease, such as colonic diversion for an obstructing colon mass. While some studies have been concerned with increased risk of adverse outcomes in older individuals, often these did not account for comorbidities, advanced cancer stage at presentation, functional impairment and other confounding factors.[22] Appropriate preoperative risk stratification must be employed. A tool developed specifically for use in older cancer patients, the Preoperative Assessment of Cancer in the Elderly (PACE), incorporates measures of cognition, functional status, depression, fatigue, ECOG performance status, American Society for Anesthesiology

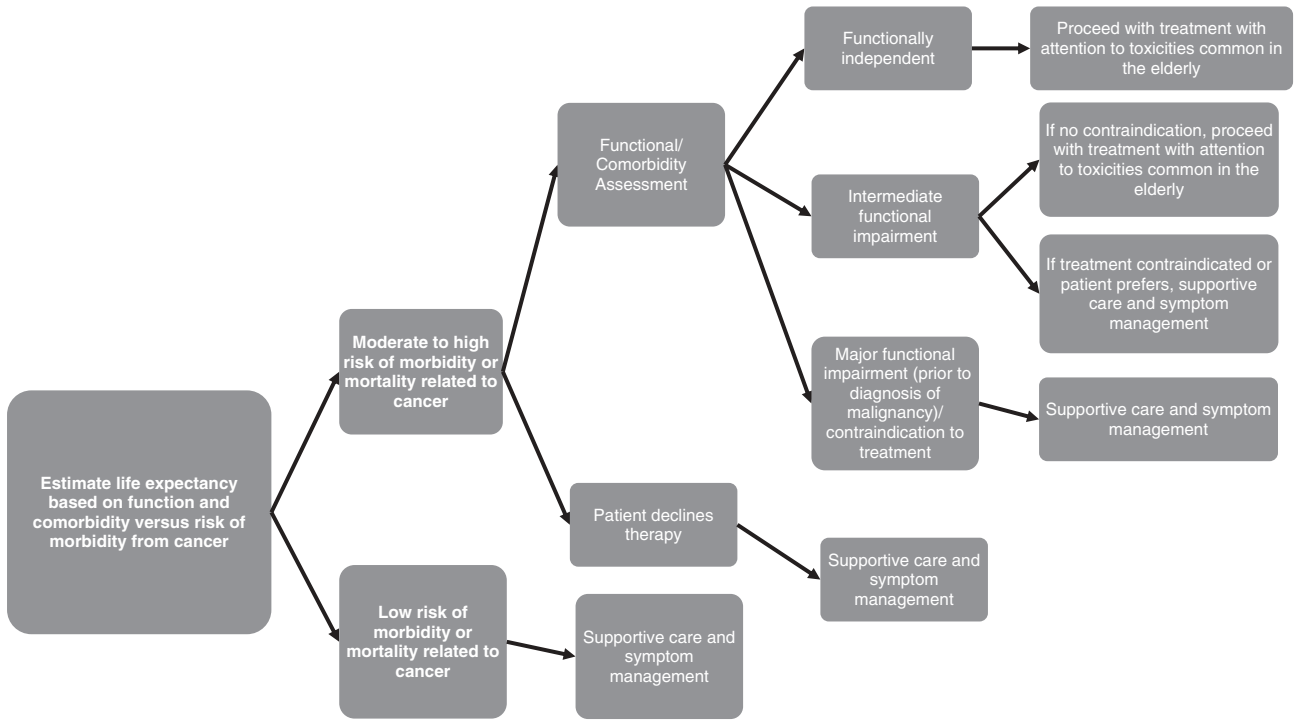

Figure 108.2 Guideline for management of senior adult oncology patients. Adapted with permission from the NCCN 1.2010 Senior Adult Oncology Clinical Practice Guidelines in Oncology. ©National Comprehensive Cancer Network, 2010. The most recent and complete version of the guideline is available at http://www.nccn.org.

scale (ASA) and Satariano's index of comorbidities. In a prospective international study of patient 70 years of age and older undergoing elective cancer surgery for solid tumours under general anaesthesia, 460 patients underwent this oncogeriatric-specific assessment on the day prior to surgery. Any dependencies in instrumental activities of daily living (IADLs), moderate to severe fatigue or abnormal performance status were associated with a 50% increased risk of 30 day morbidity following surgery. Similarly, any dependencies in ADLs or IADLs and abnormal performance status were associated with a longer than expected hospital stay; dependency in ADLs doubled the risk of an extended postoperative hospital stay.[23] Interestingly, in this study, comorbidities did not independently predict postoperative complications. Overall, older adults with cancer should not be excluded from surgery on the basis of age alone, but the decision to proceed should be individualized based on the risks of the procedure, potential benefits, the patient's functional status and goals of care.

Radiation

Radiation therapy can be employed with either curative or palliative intent. Some tumours, such as stage I lung cancers or localized prostate cancer, can be effectively treated with radiation alone. Radiation may also be used in conjunction with surgery to improve local control of cancer, as in post-lumpectomy breast irradiation for breast cancer or preoperative radiation for rectal cancer. Radiation may also provide palliation of symptoms in patients with advanced malignancies. Techniques for the delivery of radiation therapy, utilizing three-dimensional imaging reconstruction, have evolved dramatically recently, allowing improved tolerability with sparing of normal tissues. These include conformal radiation, intensity-modulated radiation and stereotactic radiation therapy. Brachytherapy involves the placement of a radioactive source directly within the site of tumour cells and is used in prostate, breast, cervical and skin cancer. Radiation may be delivered systemically in a few instances. Bone-targeting radioisotopes such as samarium-153 and strontium-89 localize to areas of osteoblastic lesions and are helpful in treating painful osteoblastic bone metastases. Radioimmunotherapy consists of radioactive isotopes conjugated to monoclonal antibodies. Examples of radioimmunotherapy include ibritumomab and tositumomab, which are used in non-Hodgkin lymphomas, target the B-cell marker CD20 and are safe and effective in older patients.

In general, there is no decrement in the benefit of radiation therapy in older compared with younger patients and no increase in toxicity in the elderly. Rectal cancer and malignant gliomas are exceptions to this statement. In older women with high-risk breast cancer, post-lumpectomy radiation improves survival. Elderly prostate cancer patients receiving radiation for localized disease have similar 10 year survival rates and disease-free survival rates compared with younger patients and should not be denied potentially curative therapy based on age alone.[24] Toxicities in the elderly are similar to those in younger patients, although older patients tend to have more functional decline acutely during therapy. In subset analyses of combination chemoradiation for lung cancer, patients over the age of 70 years tended to have more frequent oesophagitis and neutropenia, but still enjoyed a survival benefit without increased long-term complications.[25] Modern radiation techniques can also minimize long-term consequences of therapy, such as sparing the contralateral salivary glands in head and neck radiation to prevent xerostomia.

The toxicity of radiation to the brain in older patients and its effect on cognition warrant specific discussion. *Acute reactions* occur during treatment, are associated with cerebral oedema and can be controlled with corticosteroids. *Early delayed reactions* occur weeks to months after completion of radiotherapy and are characterized by somnolence and lethargy. This is associated with demyelination, endothelial damage, small-vessel thrombosis, accelerated atherosclerosis and long-term memory deficits. *Late delayed injuries* occur months to years after radiation, and are characterized by parenchymal necrosis. Patients may develop papilloedema, visual loss, hemiparesis, speech and language difficulties, seizures or dementia.[26] Despite these potential toxicities, radiation to the brain remains a cornerstone of treatment for central nervous system tumours and may provide the best option for long-term survival. The risk of cognitive changes must be balanced with the potential survival benefits.

In summary, radiation therapy can benefit older patients in both curative and palliative settings and should not be excluded from the management strategy based on the patient's age alone.

Systemic therapy

Systemic therapies include conventional cytotoxic chemotherapy, hormonal therapy, biological agents and targeted agents.

Conventional chemotherapy

Chemotherapy is generally administered intravenously, although in some cases it can be administered orally, intraperitoneally or intrathecally. Age is often considered a risk factor for toxicities and poor tolerance of chemotherapy. Indeed, the physiological changes of ageing may alter the pharmacokinetics of chemotherapeutic drugs. Mucosal changes, altered gastrointestinal motility and reduced intestinal blood flow may reduce the absorption of orally administered agents, such as capecitabine. The age-associated decrease in total body water, reduced

plasma protein concentration and lower haemoglobin concentration decrease the volume of distribution of a number of chemotherapeutic agents, increasing the risk of toxicity. Declining renal function may lead to increased toxicity of chemotherapeutic agents that are excreted renally. Changes in hepatic metabolism of chemotherapy with age have not been well studied, but ageing may be associated with increased toxicity due to drugs metabolized by the liver.[27] Polypharmacy is an important consideration, as one-third of hospitalized senior adult cancer patients take at least nine medications,[28] increasing the risk for adverse drug–drug reactions.

Pharmacodynamic effects of chemotherapeutic agents also differ in the elderly, resulting in increased risk of certain toxicities. Older patients are at increased risk of myelosuppression from chemotherapy due to decreased haematopoietic stem cell reserve (see the section below on supportive care). The increased risk of mucositis may also be attributable to a reduced ability to respond to mucosal damage. Older patients receiving anthracyclines are at increased risk for developing cardiomyopathy, which may be mitigated by limiting the total dose of anthracyclines, administering the drug by continuous infusion, using dexrazoxane (which prevents the formation of free radicals) or substituting liposomal doxorubicin. Peripheral neuropathy complicates therapy with a number of classes of chemotherapeutic agents, but is potentially reversible if the clinician monitors for its development (heralded by paraesthesias) and discontinues the offending agent before functional impairment develops.

There is significant interest in utilizing geriatric assessments to predict tolerance of chemotherapy. Preliminary reports suggest that comorbidities, depression, poor performance status and dependence in ADLs predict the development of severe toxicities of chemotherapy. There are currently several ongoing prospective studies utilizing geriatric assessments to predict tolerance of chemotherapy, the development of severe toxicities, hospitalizations and the inability to complete a course of chemotherapy.

Hormonal therapy

A number of cancers prevalent in the elderly, including breast cancer and prostate cancer, are hormonally responsive. Medications aimed at blocking these hormonal pathways can result in prevention of recurrence or prolongation of survival.

The selective estrogen receptor modulator (SERM) tamoxifen reduces the risk of recurrence by 40% and the risk of breast cancer mortality by 31% after primary treatment of estrogen receptor positive (ER+) breast cancer. The same risks of SERMs outlined in the discussion of breast cancer prevention apply, although the potential benefit is greater in the adjuvant setting. One-quarter of women are incompletely adherent to their adjuvant hormonal regimen; older age and increasing numbers of comedications are independent risk factors for non-adherence. Also of importance in the efficacy of adjuvant hormonal therapy is hepatic metabolism and polypharmacy. Tamoxifen is transformed by cytochrome P450 2D6 into the more potent anti-estrogen endoxifen. Women who receive the potent 2D6 inhibitor paroxetine concomitantly with tamoxifen are at increased risk for death from breast cancer; the benefit of tamoxifen is reduced or negated by paroxetine, likely due to reduced metabolism of tamoxifen to the more active form.[29] This interaction is not seen with other selective serotonin reuptake inhibitors.

In post-menopausal women, the aromatase inhibitors letrozole, anastrazole and exemestane are the preferred anti-estrogen therapy. Aromatase inhibitors block the conversion of adrenal androgens to estrogens by the enzyme aromatase. Several studies have shown that aromatase inhibitors either in place of or subsequent to tamoxifen are superior to tamoxifen alone as adjuvant therapy. Both tamoxifen and the aromatase inhibitors are used as first-line therapy in women with ER+ metastatic breast cancer. The aromatase inhibitors cause arthralgias and increase the risk of osteoporosis.

Testosterone fuels prostate cancer growth; thus, androgen deprivation therapy is the cornerstone of first-line therapy for metastatic prostate cancer, although over time, prostate cancer will become insensitive to anti-androgen therapy. Surgical castration was historically utilized, though medical castration is now typically preferred. The gonadotropin-releasing hormone (GnRH) agonists leuprolide and goserelin initially cause the release of FSH and LH with an increase in serum testosterone, with subsequent suppression of gonadotropin secretion. This initial testosterone release may cause increased pain in bone metastases, urinary obstruction or spinal cord compression if already impending. This tumour flare can be prevented by the administration of an androgen receptor antagonist for 2 weeks prior to GnRH agonist initiation. The GnRH antagonist degarelix causes rapid suppression of testosterone levels, but its place in the treatment of prostate cancer remains to be determined. Androgen receptor antagonists (bicalutamide, flutamide or nilutamide) are added after failure of first-line androgen deprivation therapy. Common side effects of androgen deprivation therapy are hot flushes, erectile dysfunction, gynaecomastia and anaemia. Androgen deprivation therapy is associated with an increased risk of osteoporosis.

Biological agents

Biological agents, including interleukin-2 (IL-2) and interferon, have a limited role in selected cancers such as metastatic renal cell carcinoma and melanoma. Their use in

the elderly is limited owing to their substantial toxicities. IL-2 is associated with a high likelihood of life-threatening toxicities and is generally reserved for younger patients with excellent functional status and limited comorbidities.

Targeted therapy

Over the past decade, a plethora of cancer therapeutics referred to as 'targeted therapies' have moved rapidly from preclinical development to clinical trial to clinical practice. These drugs, including monoclonal antibodies and small molecule inhibitors of tyrosine kinases, have capitalized on our growing understanding of the molecular mechanisms involved in specific malignancies. Targeting malignant cells holds the promise of less toxic treatments, which is particularly appealing in treating older patients with cancer.

Humanized monoclonal antibodies bind to cell surface receptors on the surface of the malignant cells and induce tumour cell death either by apoptosis, via antibody-dependent cytotoxicity, or through complement-mediated cytotoxicity. Infusion reactions are not uncommon with these agents and require appropriate premedication and observation.

Rituximab is a monoclonal antibody directed against the B-cell antigen CD20. A seminal trial of elderly patients (aged 60–80 years) with diffuse large B cell lymphoma randomized patients to standard combination therapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with or without rituximab. The addition of rituximab improved the complete response rate, event-free survival and overall survival with minimal additional toxicity.[30] Rituximab is now widely used in a number of B-cell malignancies, either as monotherapy in some low-grade lymphomas or in combination with chemotherapy.

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). It is utilized in combination with chemotherapy in metastatic lung, breast and colorectal cancer. However, there are increasing concerns about toxicity with bevacizumab in older patients with comorbidities. In a randomized trial, patients over the age of 70 years who received bevacizumab in combination with chemotherapy for non-small cell lung cancer had a higher incidence of bleeding, neutropenia and proteinuria compared with both older patients who received chemotherapy alone and patients under the age of 70 years receiving the same therapy, without a significant benefit in response rates or survival.[31] A pooled analysis of randomized trials of patients receiving chemotherapy with or without bevacizumab for metastatic cancer of the breast, lung (non-small cell) or colon/rectum demonstrated a twofold increased risk for arterial thromboembolic events in patients receiving bevacizumab. Risk for arterial thrombotic events was associated with a prior history thromboembolic events and age over 65 years. Aspirin use was associated with an increased risk of bleeding events.[32] Although age alone should not exclude consideration of therapy with bevacizumab, careful attention to the patient's comorbid medical conditions and medications is warranted.

Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor, utilized in metastatic colorectal cancer and squamous cell carcinoma of the head and neck. Data specific to the elderly are sparse, but in a case series of patients over the age of 70 years with metastatic colorectal cancer, therapy with cetuximab was well tolerated, with toxicities and response to therapy commensurate with those reported in clinical trials.[33]

Trastuzumab is a monoclonal antibody against the HER-2 receptor, present in up to 20% of tumours in older women with breast cancer. In clinical trials, treatment with trastuzumab improved survival in women with HER-2+ breast cancers. A retrospective cohort study of women over the age of 70 years with HER-2 over-expressing tumours who received trastuzumab in combination with chemotherapy showed response rates and survival similar to those in clinical trials, without any increased risk of toxicity compared with clinical trial cohorts.[34] It was noted that 9% of women had a 10–20% decrease in ejection fraction on serial echocardiography. Although this decline did not necessitate discontinuation of therapy, it suggests that close monitoring of cardiac status is warranted in older women receiving trastuzumab.

Imatinib inhibits the tyrosine kinase encoded by the bcr-abl oncogene, and also the receptor tyrosine kinases encoded by the c-kit and platelet-derived growth factor receptor (PDGFR) oncogenes. Imatinib is used in the treatment of chronic myelogenous leukaemia (CML), Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL) and gastrointestinal stromal tumours (GISTs). Older patients receiving imatinib for chronic-phase CML are slightly more likely to experience haematological and dermatological toxicities, but are less likely to develop oedema or neurological side effects, in comparison with their younger counterparts. Efficacy is similar, although the time to response is slightly delayed in older individuals.[35] In elderly patients Ph+ALL, imatinib is as effective at inducing remission as conventional chemotherapy, but is markedly less toxic (see Chapter 33, Management of myelodysplastic syndromes and acute leukaemia).

Erlotinib is a small-molecule inhibitor of the epidermal growth factor receptor which is used in patients with non-small cell lung cancer who have progressed after conventional chemotherapy or in whom poor performance status contraindicates chemotherapy. In a phase 3 trial of erlotinib versus placebo, older patients enjoyed a similar benefit to younger patients concerning response and survival. However, this was at the expense of a more

frequent severe toxicity, particularly rash, gastrointestinal side effects and fatigue.[36]

The tyrosine kinase inhibitor *sunitinib* is used in the treatment of advanced renal cell carcinoma and GIST. In an expanded access trial of sunitinib in advanced renal cell carcinoma, older patients experienced clinical benefit and survival similar to the entire cohort, with similar frequency of grade III–IV toxicities.[37]

Another multi kinase inhibitor, *sorafenib*, also appears to be safe and effective in older patients. Older patients with advanced renal cell carcinoma had similar response rates and similar rates of toxicities to younger patients and earlier trials.[38]

Lastly, *lapatinib* is an inhibitor of HER-1 and HER-2 indicated for the treatment of metastatic HER-2+ breast cancer. To date, no data on effectiveness or toxicity specifically in the elderly are available.

Supportive care

Senior adults receiving radiation or chemotherapy must receive aggressive supportive care to minimize the toxicities of therapy and adequately address symptoms directly related to their malignancy. Interventions that can decrease the risk of adverse events due to chemotherapy include haematopoietic growth factors, treatment of anaemia and prevention of mucositis.

Neutropenia frequently causes dose delays and dose reductions in older patients, which potentially reduces the chance of cure. Colony-stimulating factors (CSFs) or myelopoietic growth factors, including filgrastim and pegfilgrastim, decrease the incidence and duration of neutropenia and decrease the risk of neutopenic fever and hospitalization. Current recommendations include the use of CSFs for the primary prevention of febrile neutropenia when the risk of febrile neutropenia is greater than 20%. Patients at increased risk for febrile neutropenia due to age >65 years, poor performance status, poor nutritional status or serious comorbidities should receive primary prophylaxis with CSFs, even if the risk of febrile neutropenia is less than 20%.[39]

As several chemotherapeutic drugs are bound to haemoglobin in the circulation, anaemia can result in increased free fraction of cytotoxic drugs. Anaemia may also contribute to fatigue and decreased exercise tolerance. Erythropoiesis-stimulating agents (ESAs), including epoietin alfa and darbopoietin alfa, were initially embraced with enthusiasm to increase haemoglobin levels, reduce need for transfusions and improve fatigue in patients receiving chemotherapy. However, more recent data show that these agents may shorten the time to tumour progression, are associated with a 60% increase in relative risk of venous thromboembolism and are linked to a 10% increased risk of mortality [hazard ratio (HR), 1.10; 95% CI, 1.01–1.20].[40] As such, the US Food and Drug Administration (FDA) has indicated that ESAs should not be used in patients who are undergoing chemotherapy with curative intent. Current guidelines recommend discussion with the individual patient on the risks and benefits of therapy (see www.nccn.org).

In older adults, painful inflammation of the gastrointestinal tract mucosa (mucositis) is a potentially serious complication of chemotherapy. Chemotherapy drugs most commonly associated with oral mucositis include melphalan, cisplatin, 5-FU, methotrexate and cyclophosphamide. Oral mucositis impairs oral intake, causing dehydration and malnutrition. There are few effective interventions for the prevention of oral mucositis. Routine oral hygiene and bland mouth rinses, such as 0.9% saline or bicarbonate solutions, are recommended universally for the prevention and treatment of oral mucositis. Oral cryotherapy (holding ice chips in the mouth) is recommended during infusion for patients receiving stomatotoxic drugs in bolus form; it is hypothesized that vasoconstriction in the oral mucosa prevents delivery of the drug to the oral mucosa, decreasing the risk of oral mucositis.[41] Palifermin, a keratinocyte growth factor, has been approved for prevention of oral mucositis in patients undergoing stem cell transplantation, but it is not used in solid tumours. Amifostine is an organic thiophosphate approved for use in prevention of xerostomia after radiation therapy for head and neck cancer. Whether it prevents oral mucositis is controversial. The infusion can cause hypotension and it is recommended that all anti-hypertensive agents be held for 24 h prior to infusion, which may not be feasible in older adults with comorbidities. The treatment of oral mucositis includes management of xerostomia with sialogogues, management of pain with bland rinses, topical anaesthetics, systemic analgesics and prevention/treatment of superimposed infections, such as thrush.

Diarrhoea also puts patients at increased risk for dehydration; patients and their caregivers must be educated on adequate fluid intake and pre-emptive interventions. Since mucosal injury causes temporary lactase deficiency, milk products should be excluded from the diet for the duration of symptoms. Loperamide and diphenoxylate are both approved for chemotherapy-induced diarrhoea. Octreotide, the long-acting synthetic analogue of somatostatin, is reserved for patients whose diarrhoea does not respond to loperamide.

Remarkably, age over 65 years is *protective* against chemotherapy-induced nausea and vomiting. In addition, new classes of anti-emetics have dramatically reduced the incidence of chemotherapy-induced nausea. Prophylactic anti-emetics are administered with chemotherapeutic regimens having low, moderate or severe emetogenic potential. Routine prophylactic anti-emetics are not required for regimens classified as having minimal emetogenic potential.

The neurokinin (NK1) antagonist aprepitant is used as prophylaxis for highly emetogenic potential; it has no role in the treatment of breakthrough nausea and vomiting. The serotonin-5$(HT)_3$-receptor antagonists, including ondansetron, granisetron, dolasetron and palonosetron, are used in the prevention of acute nausea and vomiting, but have a limited role in the treatment of delayed nausea and vomiting. Drug interactions between these agents and the selective-serotonin reuptake inhibitors have been reported and clinicians should monitor for toxicities. In addition, constipation is a frequent side effect of drugs in this class. Although the mechanism is unknown, corticosteroids play an important role in the prevention of both acute and delayed nausea and vomiting. The dopamine $(D)_2$ receptor antagonists are widely used in both the prevention and treatment of chemotherapy-induced nausea and vomiting.[42] Extrapyramidal side effects are a dose-limiting toxicity of this class and one agent in this class, metoclopramide, has been associated with seizures in older patients with underlying seizure disorder. Benzodiazepines are commonly used for anxiolysis and prevention of anticipatory nausea and vomiting, but should be used with caution in the elderly.

Pain in older patients with cancer is frequently undertreated. Pain may be directly related to the underlying malignancy or may be chronic pain unrelated to the malignancy. Risk factors for failure to receive analgesics for daily pain include age over 75 years, minority race and impaired cognition. Management of pain in cancer patients should follow the World Health Organization Analgesic Ladder.[43] In patients for whom they are indicated, opioids are safe and effective, provided that they are initiated at a low dose and titrated slowly. Opioid-induced constipation should be universally anticipated and treated prophylactically.

The intravenous bisphosphonates pamidronate, zoledronic acid and ibandronate rapidly reduce serum calcium levels when used in treating hypercalcaemia of malignancy. They are also effective at reducing pain and the risk of skeletal-related events in patients with breast cancer metastatic to bone and in multiple myeloma. Caution should be used with the intravenous bisphosphonates when the creatinine clearance is $<30\,ml\,min^{-1}$ due to increased risk of nephrotoxicity.[44]

Multidisciplinary care models

Combining the disease-oriented approach of the medical oncologist and the patient-oriented approach of the geriatrician may improve the care of senior adults with cancer.[45] Many models for the delivery of geriatric oncology care exist. In an international panel of clinicians involved in the care of senior cancer patients, 20% reported access to a geriatrician and 34% reported that geriatric oncology was incorporated into general oncology. Among those who reported the presence of a dedicated geriatric oncology programme, 85% were located in oncology departments and 15% were located in geriatric departments. Comprehensive geriatric assessment was much more likely to be performed in institutions with a dedicated geriatric oncology programme than those without. Inpatient multidisciplinary teams usually included a medical oncologist, an advanced practice nurse, a social worker, physical therapists and, in about half of programmes, a geriatrician, nutritionist and pharmacist. Most outpatient multidisciplinary teams also included a surgical oncologist and radiation oncologist.[46]

Survivorship

With advances in cancer treatment, there are increasing numbers of older adult cancer survivors. Cancer survivors may experience long-term morbidity due to effects of the cancer itself or long-term sequelae of their therapy. Older adult cancer survivors are more likely to self-report their health as poor; they more likely to report comorbid medical conditions and functional limitations than their peers without a prior history of cancer.[47,48] In a cohort of older women followed prospectively, the prevalence of functional limitation was highest in women within 2 years of their diagnosis, but improved subsequently. Although the majority of 5-year cancer survivors in this cohort reported no functional limitations, they were more likely to report limitation in activities that required strength and mobility, such as heavy work, walking half a mile or walking up and down stairs, than their peers who had no history of cancer.[49] Studies differ on whether cancer survivors have an increased prevalence of psychological disorders.

Cognitive changes temporally associated with cancer treatment, colloquially known as 'chemobrain', are an area of debate. Early reports of selected younger women following adjuvant chemotherapy for breast cancer revealed an association between chemotherapy and impairments on neuropsychological testing, relative to population norms or controls.[50,51] However, these studies were potentially confounded by a number of factors, including depression and hormonal therapy. Although half of older women reported a subjective decline in their cognitive function 6 months after chemotherapy, prospective longitudinal studies have shown a decline in cognitive testing in only one-quarter of women at 6 months of follow-up.[52,53] Other studies showed no difference in change in neuropsychological testing between patients and controls over time.[54] A large population-based study of people over the age of 65 years showed no difference in the frequency of self-reported memory problems or positive screens for cognitive impairment between long-term cancer survivors and controls.[48] To date, an association between chemotherapy and functional

decline due to cognitive impairment in senior adult cancer survivors has not been established. Brain radiotherapy for central nervous system tumours is clearly associated with cognitive decline; older patients are at particularly increased risk for brain atrophy and dementia following brain radiotherapy.[26] Cognitive sequelae of therapy will be an area of continued interest as the number of senior adult cancer survivors increases.

A history of receiving chemotherapy or radiation therapy increases the risk for additional medical problems. Certain chemotherapeutic agents, including the alkylating agents and topoisomerase II inhibitors, are associated with the development of myelodysplastic syndrome and acute myeloid leukaemia. Radiation increases the risk of bone and soft tissue sarcomas within the radiation field. Women who underwent mediastinal radiation for Hodgkin lymphoma are at increased risk for breast cancer. There is also an increased risk of coronary artery disease following mediastinal radiation in early adulthood. Physicians caring for long-term cancer survivor patients must be aware of potential long-term complications of their prior therapy, including second malignancies.

Conclusion

Cancer in the elderly is a growing problem. Older individuals are likely to be diagnosed at a more advanced stage and to receive substandard treatment for their cancer, although there is a growing body of literature showing that older adults may benefit from cancer treatment to the same degree as younger patients.

Biological changes associated with ageing are associated with increased risk of developing cancer. Strategies for prevention of cancer are promising, but most are not widely utilized due to potential risks of treatments. Decisions about screening for common cancers should be individualized, taking into account a patient's wishes, functional status, comorbidities and whether they would be eligible for treatment of a cancer detected during screening.

There is little reason why an older patient should be excluded from treatment of their cancer based on age alone. Again, decisions should be individualized based on a comprehensive assessment of the patient's health status. Geriatric assessments can predict which patients are at increased risk for postoperative morbidity and prolonged hospitalization following cancer surgery. Radiation therapy is well tolerated in elderly patients. Cytotoxic chemotherapy can be tolerated without difficulty in many older patients; results of studies using geriatric assessments to predict which patients are at increased risk for toxicities are eagerly awaited. Targeted therapies are emerging as acceptable, potentially less-toxic options for patients who are not candidates for conventional cytotoxic chemotherapy. Aggressive supportive care with attention to the toxicities most commonly seen in the elderly, such as myelosuppression, will allow older patients to receive treatments with fewer delays or dose reductions, which could otherwise reduce the effectiveness of treatment.

With improvements in survival, there is a burgeoning population of older adult cancer survivors. Some of these patients will have residual functional limitations or cognitive decline following completion of their treatment. Treatments may leave patients at increased risk for secondary malignancies or the development of secondary comorbidities over time.

Multidisciplinary care with the collaboration of geriatricians, medical oncologists, radiation oncologists, surgical oncologists, pharmacists, social workers, nurses and physical and occupational therapists may optimize the treatment of elderly cancer patients.

Key points

- With the growth of the aged segment of the population and the increased incidence of cancer in the elderly, the problem of cancer in the elderly is growing. The historical undertreatment of older adults with cancer must be re-examined, as many older patients with cancer can be safely treated with meaningful prolongation of survival.
- Decisions to pursue cancer screening in the elderly must be individualized based on the patient's life expectancy, functional status, comorbidities and preferences.
- Advanced age is, in general, not a primary consideration for determining surgical risk. Geriatric assessment predicts which older patients are at increased risk for postoperative morbidity. Radiation is well tolerated in older patients and improved techniques further minimize toxicity by sparing normal tissue.
- The decision to utilize systemic cytotoxic chemotherapy depends on the patient's preferences, functional status, comorbidities and goals of therapy. Haematopoietic growth factors decrease the risk of complications associated with neutropenia. Targeted therapies may offer less-toxic treatment options. Polypharmacy must be monitored, as comedications may decrease the efficacy of the anti-cancer treatment, as has been shown with paroxetine and tamoxifen.
- Senior cancer survivors may have unique challenges following therapy and be at increased risk for complications ranging from osteoporosis to dementia to treatment-related acute leukaemia.

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CHAPTER 109

Oncological emergencies

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Introduction

Most cancer patients experience at least one emergency during the course of the disease. An ageing population is resulting in more people being diagnosed with cancer and an increasing number of treatment options means that many patients live significantly longer with their disease. It is anticipated, therefore, that an increasing number of patients will present to primary and secondary care with acute complications of cancer or the treatment thereof. Physicians should be familiar with oncological emergencies as failure to implement immediate and appropriate treatment may result in significant morbidity or death. This chapter focuses on the common and critical complications of cancer (Table 109.1) in older adults.

Haematological emergencies

Haematological emergencies include febrile neutropenia, thrombocytopenia, intravascular disseminated coagulation and hyperviscosity syndrome.

Febrile neutropenia

Neutropenia is usually defined as an absolute neutrophil count (ANC) of $<500 \times 10^9$ cells l^{-1}. Fever in neutropenic patients is usually defined as a single temperature of $>38.3\,^{\circ}C$ ($101\,^{\circ}F$) or a sustained temperature $>38\,^{\circ}C$ ($100.4\,^{\circ}F$) for more than 1 h. However, absence of fever in neutropenic patients does not mean absence of infection, for example,. in the case of corticosteroid use or in elderly patients. A thorough general physical examination should be performed and repeated to identify the infection source: in the absence of neutrophils, signs of inflammation can be extremely subtle, and hypothermia, hypotension or clinical deterioration should be recognized as the initial signs of occult infection. Identified risk factors for occult infection include severe neutropenia, rapid decline in ANC, prolonged duration of neutropenia (>7–10 days), cancer not in remission and comorbid illnesses requiring hospitalization.[1] Approximately 80% of identified infections are believed to arise from patients' own endogenous flora.

Broad-spectrum antibiotics should be given as soon as possible and at full doses (adjusted for renal and/or hepatic function), to avoid the 70% mortality related to the delay of initiation of antibiotics.

Initial antibiotic selection should be guided by the patient's history, allergies, symptoms, signs, recent antibiotic use and culture data and awareness of institutional nosocomial infection pattern. There is no clear optimal choice for empirical antibiotic therapy.[2] Combination therapy and monotherapy (cefepime, ceftazidime) have led to similar outcomes. In critically ill patients, an aminoglycoside should be added for better Gram-negative coverage or a fluoroquinolone or aztreonam when renal function is a cause for concern. (Table 109.2).

In certain circumstances, a drug active against Gram-positive bacteria is recommended. Such circumstances include known colonization with Gram-positive bacteria, suspected infection of a central venous line or device and severe sepsis with or without hypotension. Gram-positive bacteria should also be considered in patients with suspected skin infection or severe mucosal damage and when prophylactic antibiotics against Gram-negative bacteria have been used.[3]

In the case of persistent fever after 5 days without an identifiable source, the following options are valuable:

- Continuing treatment with the initial antibiotic(s) if the patient is clinically stable and the neutropenia is expected to resolve within the ensuing 5 days.
- Changing or adding antibiotic(s) if there is evidence of progressive disease or a new complication (onset of abdominal pain due to enterocolitis, pulmonary infiltrates or drug toxicity).

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 109.1 Summary of oncological emergencies.

Emergency	Cause	Clinical findings
Haematological		
Febrile neutropenia	Chemotherapy-associated bacterial or fungal infections	Temperature >101 °F (38.3 °C), absolute neutrophil count <500 mm^{-3} (0.5×10^9 l^{-1})
Thrombocytopenia	Chemotherapy-induced toxicity, disseminated intravascular coagulation, bone metastasis	Bleeding, platelet count $<150 \times 10^9$
Disseminated intravascular coagulation	Metastatic disease	Thrombotic events, Trousseau syndrome, diffuse bleeding
Hyperviscosity syndrome	Waldenström macroglobulinaemia, myeloma, leukaemia	Spontaneous bleeding, retinal haemorrhage, neurological defects, Raynaud syndrome, congestive heart failure, serum viscosity levels >5
Metabolic		
Hypercalcaemia	Lung, breast, prostate and renal cancer, myeloma	Apathy, malaise, weakness, confusion, polyuria–polydipsia, evolving anorexia with nausea plus constipation, renal failure, coma, ECG modifications
Syndrome of inappropriate antidiuretic hormone	Lung cancer	Anorexia, nausea, vomiting, constipation, muscle weakness, myalgia, polyuria-polydipsia, severe neurological symptoms (e.g. seizures, coma)
Tumour lysis syndrome	Haematological malignancies, small-cell lung cancer	Azotaemia, acidosis, hyperphosphataemia, hyperkalaemia, acute renal failure, hypocalcaemia
Neurological		
Spinal cord compression	Breast, lung, renal and prostate cancers and myeloma	New back pain that worsens when lying down, late paraplegia, late incontinence and loss of sensory function
Delirium	Drugs, infection, anaemia, dehydration, surgery, pain	Impairment of consciousness, cognitive impairment of acute onset, disorientation, disturbance of the sleep–wake cycle, illusions, hallucinations
Brain metastases and increased intracranial pressure	Lung cancer, breast cancer, melanoma	Symptoms can be focal or generalized and depend on the location of the lesion within the brain (headaches, seizures, hemiparesis, cognitive disturbance, ataxia)
Cardiologic		
Superior vena cava syndrome	Lung cancer, metastatic mediastinal tumours, lymphoma, indwelling venous catheters	Cough, dyspnoea, dysphagia, head, neck or upper extremity swelling or discoloration, development of collateral venous circulation
Pericardial effusion	Metastatic lung and breast cancer, leukaemia, lymphoma	Dyspnoea, fatigue, distended neck veins, distant heart sounds, tachycardia, orthopnoea, narrow pulse pressure, pulsus paradoxus, water-bottle heart
Structural		
Airway obstruction	All the malignancy from the base of the tongue to the terminal bronchiole	Dyspnoea, stridor (extrathoracic obstruction), wheezing, sudden respiratory distress

Table 109.1 (*continued*).

Emergency	Cause	Clinical findings
Bowel obstruction	Abdominal and gynaecological tumour, mesenteric metastasis	Abdominal pain and distension, vomiting, lack of intestinal emissions
Urinary obstruction	Urinary and gastrointestinal tract cancer, mesenteric metastasis	Flank pain and tenderness, nausea/vomiting, fever, chills, haematuria and oliguria/anuria
Pathological fractures	Breast, lung, prostate, myeloma, thyroid	Bone pain

Table 109.2 Initial antibiotic therapy of neutropenic fever.

Type of therapy	Treatment[a]
Monotherapy	Cefepime Ceftazidime Carbapenem Piperacillin/tazobactam
Combination	Aminoglycoside (or quinolone) + one of the following drugs: Piperacillin Cefepime Ceftazidime Carbapenem

[a]In certain circumstances (e.g. suspected infection of a central venous line or device, skin infection, severe mucosal damage), a drug active against Gram-positive bacteria is recommended. Vancomycin is also the most commonly used drug for suspected infections with Gram-positive bacteria. Reproduced with permission from Halfdanarson *et al*.[3]

• Adding an antifungal drug, with or without changing the antibiotics, if the neutropenia is expected to persist for more than 5–7 days.

If an infectious source of fever is identified, antibiotics should be continued for at least the standard duration (e.g. 14 days for bacteraemia). With no known source, the timing of the discontinuation of antibiotics is usually dependent on resolution of fever and neutropenia. If the ANC increases to $>500 \times 10^9$ cells l^{-1} and the patient becomes afebrile, antibiotics are usually administered for 7 days.

In older patients, primary prophylactic colony-stimulating factor was observed to be effective in reducing the incidence of neutropenia and infection.[4]

Thrombocytopenia

Thrombocytopenia (platelet count $<150 \times 10^9\,l^{-1}$) is mainly a consequence of myelotoxicity induced by chemotherapy[5] or less frequently by radiotherapy, and rarely a sign of disseminated intravascular coagulation. In addition, certain malignant conditions are associated with immune-mediated thrombocytopenia. Multiple causes of thrombocytopenia may coexist in a given patient.

In the case of chemotherapy, neutropenia almost invariably accompanies the low platelet count. If the degree of thrombocytopenia occurs more rapidly or is more severe or more prolonged than anticipated, then a second mechanism should be suspected. The presence of bone marrow metastases should be suspected if anaemia or thrombocytopenia are observed prior to treatment or if chemotherapy induces a sudden or excessive fall in the haemoglobin or platelet count. Immune-mediated destruction of platelets is commonly seen with lymphoid malignancies. As a general rule, patients with autoimmune thrombocytopenia experience less bleeding for a given platelet count compared with patients with chemotherapy-induced thrombocytopenia or other mechanisms of bone marrow failure.

If there is no obvious relationship between platelet count and administration of chemotherapy, a bone marrow aspirate and trephine examination may be indicated. In immune-mediated thrombocytopenia, plentiful megakaryocytes are expected since platelet destruction occurs in the peripheral circulation. If bone marrow metastasis is the primary mechanism of thrombocytopenia, the bone marrow trephine is the most sensitive diagnostic tool.

Patients who have a platelet count of above $10 \times 10^9\,l^{-1}$ with absence of bleeding may be managed conservatively, provided that they have a full daily clinical examination including fundal examination. In the absence of bleeding and of evidence of sepsis or coagulopathy, then observation is adequate.

Platelet counts below $10 \times 10^9\,l^{-1}$ or bleeding need random donor platelets. It should be remembered that the key end point is to arrest the bleeding, and this may occur without a significant platelet rise. However, failure to obtain the expected platelet rise after two consecutive transfusions (platelet refractoriness) may be due to conditions that cause increased platelet consumption (e.g. fever, splenomegaly) or may be related to human leukocyte antigen (HLA) alloimmunization from previous transfusions or pregnancies.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a clinical syndrome characterized by systemic activation of

coagulation leading to intravascular deposition of fibrin and thrombosis of small vessels. Depletion of natural anticoagulants such as protein C and antithrombin and suppression of fibrinolysis also add to the prothrombotic state. In addition, there may be consumption of multiple coagulation factors and platelets leading to bleeding. The delicate balance between factors that promote thrombosis and factors that lead to bleeding will determine the clinical presentation of the patient.

Clinical evidence of DIC is seen in 10–15% of patients with metastatic cancer and laboratory markers are found in 50–70% of patients (increased levels of fibrinogen, fibrin degradation products and coagulation factors V, VIII, IX and XI).

There is no single diagnostic test for DIC. The presence of a prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) with elevated levels of D-dimers and a low or low-normal fibrinogen in a clinical setting known to be associated with DIC will confirm the diagnosis in a bleeding patient. A blood film may show fragmented red blood cells. Patients with thrombosis may have a shortened PT and APTT, a high or high-normal fibrinogen and elevated D-dimers. All features may not be present in every patient. Serial tests are required to monitor progression of the condition and response to therapy and to direct further treatment.

The essence of action is supportive care.[6] Removal of the underlying precipitant is advised. Therefore, the tumour should be treated where possible and concomitant sepsis should be managed aggressively. Random donor platelets should be given until the platelet count is $>20 \times 10^9\,l^{-1}$ or until bleeding has stopped. If bleeding is life-threatening, then the platelet count should be raise to $50 \times 10^9\,l^{-1}$. Fresh frozen plasma (FFP) containing all coagulation factors including fibrinogen and von Willebrand's factor is indicated for bleeding with a prolonged PT and APTT.

Hyperviscosity syndrome

Hyperviscosity is defined as an increased intrinsic resistance of fluid to flow. Marked elevations in paraproteins, marked leukocytosis or erythrocytosis in some cancer patients can result in elevated serum viscosity and the development of significant sludging, decreased perfusion of the microcirculation and vascular stasis with the development of the hyperviscosity syndrome. Common causes of the hyperviscosity syndrome include Waldenstrom macroglobulinaemia, multiple myeloma and leukaemias. Clinical manifestations of the hyperviscosity syndrome, most apparent with a serum viscosity >5 (the relative viscosity of normal serum ranges between 1.4 and 1.8), include a triad of bleeding, visual disturbances and neurological manifestations (Table 109.1). Management of hyperviscosity should aim at urgent reduction of serum viscosity in symptomatic patients by leukopheresis or plasmapheresis. This should be followed by specific chemotherapeutic agents to treat the underlying disease after relief of symptoms. Temporary measures should focus on adequate rehydration and, in patients with coma and established dysproteinaemia, a two-unit phlebotomy with replacement of the patient's red blood cells with physiological saline should be performed.

Metabolic emergencies

Metabolic emergencies include hypercalcaemia, hyponatraemia and tumour lysis syndrome.

Hypercalcaemia

Tumour-induced hypercalcaemia, the most common metabolic emergency in patients with cancer, is due to skeletal metastases or to a paraneoplastic syndrome related to parathyroid hormone-related protein. Hypercalcaemia has been reported in 10–30% of patients with cancer at some time during their disease.[7]

The symptoms of hypercalcaemia are multiple and nonspecific. Classic symptoms include lethargy, confusion, anorexia, nausea, constipation, polyuria and polydipsia (Table 109.1).

Symptoms vary depending on the degree of hypercalcaemia and the rapidity of onset.[8] Changes in mental faculties and strength are more easily recognized in younger individuals, whereas in the elderly such events can be easily blamed on many things, including their poor tolerance of analgesics, anxiolytics, hypnotics and antiemetics.

The definition of hypercalcaemia is an elevation of calcium level above $2.64\,mmol\,l^{-1}$ ($10.6\,mg\,dl^{-1}$) and values above $2.74\,mmol\,l^{-1}$ ($11.0\,mg\,dl^{-1}$) should be considered an indication to initiate treatment. This threshold should be considered (according to the range of normal values from a local laboratory) only in the case of a normal albumin level. If there is any doubt about the validity of the total serum calcium level, measurement of ionized calcium or calculation of the adjusted calcium level to albumin concentrations is essential.

Asymptomatic patients with minimally elevated calcium levels ($<3\,mmol\,l^{-1}$) may be treated as outpatients with encouragement to adopt oral hydration, mobilization and elimination of drugs that contribute to hypercalcaemia (thiazides, lithium). Patients who are symptomatic or have calcium levels $>3\,mmol\,l^{-1}$ should be considered for inpatient management using volume expansion with saline infusion, corticosteroids and bisphosphonates, as follows:

- Rehydration generally has mild and transient effects on calcium levels. The volume of saline infusion depends on the extent of the hypovolaemia and also the patient's cardiac and renal function.

• Bisphosphonates[9] have supplanted all other drugs except calcitonin, still useful in the few cases of severe refractory hypercalcaemia because of its rapid onset of action (2–4 h versus 72 h for bisphosphonates). The recommended dose is 90 mg i.v. over 2–4 h for pamidronate or 4 mg i.v. over 15 min for zoledronate. In patients with pre-existing renal disease, no change in dosage, infusion time or interval is required.
• Glucocorticosteroids can be helpful in the management of hypercalcaemia caused by lymphoma, myeloma and sometimes breast cancer and may be of some value in other malignancies, used at doses of 10–100 mg per day equivalent prednisone.

Hyponatraemia

Serum sodium levels below 135 mmol l^{-1} (135 mequiv l^{-1}), especially with rapid fall, can lead to brain oedema with altered mental status, lethargy, seizures, coma and death. Routine evaluation of serum electrolytes is mandatory in patients with otherwise unexplained alterations of mental status.

Aetiologies are iatrogenic complication[10] (vasopressin, chlorpropamide, carbamazepine, clofibrate, vincristine, ifosfamide and narcotics), water redistribution associated with mannitol infusions, pseudo-hyponatraemia due to hyper-para-proteinaemia or hyperlipidaemia and acute water intoxication, renal sodium loss due to diuretic therapy, extra-renal sodium loss during vomiting/diarrhoea, sudden withdrawal of glucocorticoid therapy and syndrome of inappropriate antidiuretic hormone (SIADH).[11]

SIADH can cause a severe decrease in sodium that may be life-threatening. Diagnostic features include hypo-osmolality of serum, inappropriately high osmolality of urine for the concomitant plasma hypo-osmolality, continued renal excretion of sodium (Table 109.3), associated with clinical normovolaemia, and normal renal, adrenal and thyroid function.

SIADH is a paraneoplastic condition associated with small-cell carcinoma of the lung, central nervous system disease (e.g. metastases, infection and haemorrhage) and pulmonary disorders (e.g., metastases, infection).

Table 109.3 Diagnostic criteria of syndrome of inappropriate antidiuretic hormone (SIADH).

Criterion	Definition
Hyponatraemia	Plasma sodium <135 mequiv l^{-1}
Hypo-osmotic plasma	Plasma osmolality <280 mOsm kg^{-1}
Hyperosmotic urine	Urinary osmolality >500 mOsm kg^{-1}
Hypernatraemic urine	Urinary sodium >20 mequiv l^{-1}

Symptoms depend on the depth and the rate of development. However, elderly patients are more susceptible and may manifest cognitive impairment with less deep hyponatraemia. However, in elderly patients it is difficult to distinguish the hyponatraemia due to SIADH from other causes which are multiple.

The major focus of treatment for SIADH is successful treatment of the underlying disease by chemotherapy and/or radiotherapy. Acute treatment is indicated in patients who have severe hyponatraemia (e.g. plasma sodium <125 mequiv l^{-1}) and who are symptomatic. The goals of therapy are to initiate and maintain rapid diuresis with i.v. furosemide, while restricting the 'free water' intake to 500–1000 ml per day and to replace the sodium and potassium lost in the urine by administering 0.9% saline infusions with added potassium. This rapid correction should not exceed a 20 equiv l^{-1} rise in serum sodium concentration during the first 48 h (1 mequiv l^{-1} h^{-1}) to avoid neurological damage and central pontine myelinolysis.

Tumour lysis syndrome

Tumour lysis syndrome is the set of metabolic abnormalities that results from acute destruction of neoplastic cells and release of their intracellular products into the circulation.[12] The high rate of cell turnover overwhelms the body's normal homeostatic mechanisms for handling potassium, calcium, phosphorus and uric acid, leading to hyperuricaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia and uraemia. These may be seen alone or in combination with one another.

Also, the release of intracellular purines from fragmented tumour nuclei increases serum uric acid. Uric acid, with a pH of 5.4, exists in a soluble form at physiological pH. However, in the acidic environment of the kidney collecting ducts, uric acid may crystallize in the collecting ducts and ureters. This may lead to an obstructive nephropathy and subsequent renal failure. In addition, purine precursors including adenosine triphosphate, adenosine diphosphate and adenosine regulate vascular tone. With elevation of angiotensin II, adenosine may lead to preglomerular vasoconstriction and postglomerular vasodilatation with a resultant reduction in filtration and renal failure. The risk of renal failure may be increased in the setting of renal parenchymal tumour infiltration or ureteral or venous obstruction from tumour compression. Hyperkalaemia associated with tumour lysis syndrome may be accentuated by associated renal insufficiency and may cause electrocardiographic alterations and potentially fatal cardiac arrhythmia. The major manifestation of hyperphosphataemia is secondary hypocalcaemia caused by precipitation of calcium phosphate in the soft tissues, which may present as renal failure, pruritic or gangrenous changes in the skin or inflammation of the eyes or joints. Signs and

symptoms of hypocalcaemia include anorexia, vomiting, cramps, carpopedal spasms, tetany, seizures, alterations in consciousness, cardiac dysrhythmia and occasionally cardiac arrest.

The syndrome is commonly iatrogenic, caused by administration of therapy during the rapid growth phase of aggressive malignancies (high-grade lymphomas, leukaemia patients with high leukocyte counts, less frequently solid tumours).

Patients at risk are men with advanced disease, markedly elevated lactate dehydrogenase level with predisposing factors including volume depletion, concentrated acidic urine pH and excessive urinary uric acid excretion rates.

The diagnosis is based on the development of increased levels of serum uric acid, phosphorus and potassium, decreased levels of serum calcium and oliguric renal failure following chemotherapy.

The incidence of tumour lysis syndrome is rare, due to the use of prophylactic measures in patients at risk: adequate hydration, urine alkalinization, use of allopurinol started 24–48 h before initiation of cytotoxic treatment, monitoring of serum electrolytes, uric acid, phosphorus, calcium and creatinine levels.

Treatment of established tumour lysis syndrome is directed at vigorous correction of electrolytic abnormalities, hydration and haemodialysis (as appropriate in patients with renal failure).

Cardiovascular emergencies

Cardiovascular emergencies include superior vena cava syndrome, cardiac tamponade, venous thromboembolic complication and volume depletion.

Superior vena cava syndrome

Large space-occupying lesions in the upper mediastinal space may compress the superior vena cava (SVC), obstructing the return of blood to the heart. SVC syndrome is seen mainly with (small-cell) lung cancer, lymphoma and mediastinal metastasis of solid tumours or with thrombosis, commonly related to intravascular device complication.

Typically, SVC syndrome produces cough, dyspnoea and dysphagia combined with swelling and discoloration of the neck, face or upper extremities. Depending on the site of the disease, both vocal cord paralysis and Horner syndrome can occur. Clinical findings are greater in complete obstruction than in mildly obstructive disease or in gradual obstruction. Others symptoms may include hoarseness, dysphagia, headaches, dizziness, syncope, lethargy and chest pain. They may be worsened by positional changes, particularly bending forward, stooping or lying down. Physical findings include oedema of the face (periorbital, laryngeal, glossal oedema), neck or arms, dilatation of the veins of the upper body, plethora or cyanosis of the face and mental status changes.

Treatment of tumour-related SVC syndrome includes radiotherapy, chemotherapy or expandable wire stents.[13] For patients known to have small-cell carcinoma of the lung or lymphoma, chemotherapy is the treatment of choice. Life-threatening symptoms, such as respiratory distress, are indications for urgent radiotherapy. The usefulness of anticoagulation must be weighed against the risk of haemorrhage in a venous system under increased pressure. Placement of an expandable wire stent across a stenotic portion of the vena cava is an appropriate therapy when possible. Diuretics and steroids may provide transient symptomatic relief of oedema and respiratory compromise, although no controlled trials support their use.

Catheter-associated SCV thrombosis is best treated by immediate thrombolytic therapy, administered when possibly directly to the thrombus to minimize systemic fibrinolysis. An alternative is anticoagulation and catheter removal.

Cardiac tamponade

Tamponade occurs when fluids accumulate faster than the pericardium can stretch. Compression of all four chambers ensues, with tachycardia and diminishing cardiac output. Dyspnoea is the most common symptom, often with cough or retrosternal chest pain (Table 109.1). There are often distant heart sounds, pulsus paradoxus and pericardial friction rub. With cardiac tamponade, progressive heart failure occurs, with increased shortness of breath, confusion and hypotension.

Asymptomatic, small effusions may be managed with careful follow-up and treatment directed against the underlying malignancy.[14] Cardiac tamponade requires an immediate removal of pericardial fluid as an emergency, under echocardiographic guidance, to ensure symptom relief and cytological diagnosis. In patients with symptomatic, moderate to large effusions who do not present as an emergency, therapy should be aimed at relieving symptoms and preventing recurrence of tamponade. After pericardiocentesis alone, effusion usually recurs rapidly. Percutaneous tube drainage can be performed in addition to pericardial windows or resection, based on the underlying condition of the patient.

Venous thromboembolic complications

Cancer increases the risk of venous thromboembolism (VTE) 4–6-fold. The aetiology of deep venous thrombosis (DVT) and pulmonary embolism (PE) in cancer patients may be attributable to several factors: hypercoagulable states due to abnormalities of blood composition (increased plasma levels of clotting factors, cancer procoagulant A,

tissue factors and cytokines) and increased release of plasminogen activator, and indwelling central venous catheter. Chemotherapy agents also increase endothelial cell reactivity to platelets, a phenomenon which may underlie thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome.

Initial treatment[15] of acute VTE starts with heparin, either unfractionated heparin (UFH) or low molecular weight heparin (LMWH), followed by a coumarin derivative (e.g. warfarin). UFH is administered as a bolus followed by a continuous drip, titrated to approximately partial thromboplastin time (PTT) 1.5–2 times control. Oral anticoagulants are usually started on day 1 or 2 of treatment, are monitored by PTT and dosages are adjusted to maintain an international normalized ratio (INR) between 2.0 and 3.0. Patients are maintained on UFH for 4–5 days while the oral anticoagulant is titrated to therapeutic levels. The use of LMWH is easier and does not need laboratory monitoring, except for individuals with renal insufficiency or those with <50 kg body weight or with obesity (plasma anti-factor Xa concentration). LMWH is the treatment of choice in patients receiving chemotherapy since many drugs may alter the anticoagulant response to oral anticoagulants.

Catheter-related thrombosis is treated with fibrinolytic agents (tissue-type plasminogen activator, streptokinase or urokinase). Pre-existing clotting defects, bleeding source, central nervous system metastatsis, recent major surgery and a history of gastrointestinal bleeding or uncontrolled hypertension are contraindications to thrombolytic treatment. Patients who develop recurrent thrombosis while on therapeutic doses of anticoagulation should be considered for inferior vena cava filter placement.

Age alone is not a contraindication to appropriate thrombolytic therapy or anticoagulation, although it may complicate management (e.g. risk of fall, gastrointestinal bleeding and variable appetite and diet).

Volume depletion

Often overlooked, dehydration is very common in cancer patients and volume depletion may lead to hypovolaemic shock more rapidly in elderly than in younger individuals due to a limited reserve of body water and a blunted response of capacitance vessels to sympathetic stimulation. Many studies have reported greater severe 5-fluorouracil-induced toxicity related to advanced age.[16,17] The mechanism does not result from decreased clearance of chemotherapy but from age-related impairment of compensatory mechanisms including a cascade of secondary effects related to poor physiological reserves. Mucositis, leading to dysphagia and diarrhoea, is highlighted among the causes of volume depletion in the elderly. Unfortunately, the presentation of volume depletion may be delayed, including poor appreciation of the initial symptoms of mucositis, inadequate fluid replacement due to swallowing disorders and inadequate access to transportation.

The mainstay of the management of fluid depletion includes timely fluid resuscitation. Early management may prevent both death and complications such as functional dependence.

Neurological emergencies

Neurological emergencies include brain metastases, increased intracranial pressure, spinal cord compression and delirium.

Brain metastases and increased intracranial pressure

Intracranial metastases occur in up to one-quarter of patients dying of cancer.[18] Brain metastases arise from haematologenous spread of the tumour and the distribution within the brain is in accordance with the regional blood flow. Approximately 90% of brain metastases are found in the supratentorial region. The metastases are commonly located at the junction of the grey and white matter and in the so-called watershed areas of the brain. Brain oedema and tumour expansion commonly result in increased intracranial pressure.

In patients with intracranial-occupying lesions (brain tumours, metastases, oedema), the intracranial pressure may rise to 25–30 mmHg, leading to hypoperfusion and to death. Clinical findings (Table 109.1) depend on the rate of the rise in intracranial pressure and signs depend on the lesion's topography. Conservative treatment is aimed reducing vasogenic oedema and maintaining cerebral perfusion thanks to patient position, control of arterial blood pressure, hypertonic infusions (mannitol 20%, 1 g kg^{-1} in 15–30 min twice per day for 3 days) and corticosteroids (dexamethasone 4 mg four times per day).

Spinal cord compression

Spinal cord compression, due to extradural tumour mass, usually resulting from involvement of the vertebral column, is not immediately life-threatening unless it involves level C3 or above, but it may lead to profound, permanent morbidity. Paraplegia or loss of sphincter control or both not only diminishes a patient's quality of life but also predisposes to further complications such as venous thrombosis, decubitus ulcers and urinary obstruction. It often presents insidiously with back pain radiating in a belt-like fashion and may progress rapidly to overt neurological dysfunction (weakness and sensory loss), leading to irreversible paralysis.

Treatment outcome correlates with the degree and duration of neurological impairment prior to therapy. The

choice of treatment[19] depends on the clinical presentation, rapidity of the clinical course, type of malignancy, site of spinal involvement and previous treatment. Corticosteroids (dexamethasone 10 mg intravenously followed by an oral dose of 16 mg daily) are used until efficacy of definitive treatment, radiotherapy (30 Gy in 10 fractions over 2 weeks) or surgical decompression (laminectomy or vertebral body resection) in selected patients.

Delirium

Delirium remains the most common and distressing neuropsychiatric complication in patients with advanced cancer. Delirium is defined as an acute, transient, fluctuant and usually reversible cause of cerebral dysfunction and manifests clinically with a wide range of psychiatric abnormalities. The cause of hospitalization for 10–22% of elderly patients, delirium has been found in 14–56% of elderly medical inpatients[20] and even more in intensive care units (41–87% of patients).[21]

Delirium is associated with an increased risk of mortality not only during the stay but also[22] during the months following discharge.[23] The consequences of delirium include not only increased mortality but also lengthened hospital stays and the need for increased services after hospital discharge.

Unfortunately, delirium is often unrecognized by the patients' physicians and nurses,[24,25] because of its fluctuating nature, its overlap with dementia, lack of formal cognitive assessment and under appreciation of its clinical consequences.

The clinical features of delirium are numerous and encompass a variety of neuropsychiatric symptoms common to other psychiatric disorders. Delirium or acute confusional state is characterized by impairment of consciousness and global cognitive impairment of acute onset. Other key features include disorientation and disturbance of the sleep–wake cycle. Psychomotor behaviour may be altered. Patients may be hypoactive or hyperactive; in the latter case patients can be agitated and even physically combative. Perception can be altered with patients experiencing illusions (misinterpretations of external stimuli, for example, believing that patterns in the bed sheets are insects) or hallucinations (perceptions in the absence of stimuli). Frank paranoid ideas or delusions may occur. The syndrome is frequently worse at night and periods of relative lucidity can occur.

Several delirium assessment and rating scales have been designed to aid clinicians in the diagnosis of delirium, such as the Confusion Assessment Method (CAM).[26]

The pathophysiology of delirium remains poorly understood, but perturbations of neurotransmitters (cholinergic balance) may play a role.[27,28] Given the clinical heterogeneity and multifactorial nature of delirium, it is likely that multiple pathogenic mechanisms contribute to its development, with a complex interrelationship between vulnerability (patient with predisposing factors) and exposure to precipitating factors or noxious insults: in vulnerable patients (e.g. those with dementia and multiple coexisting conditions), delirium may develop as a result of relatively benign insults, such as one dose of a sleeping medication. Conversely, delirium may develop in patients who are not vulnerable after exposure to multiple noxious insults, such as general anaesthesia, major surgery and psychoactive medications (Table 109.4).

In a recent series of 100 cancer patients, the aetiology of delirium was multifactorial (two or more in 40% of patients) and the 1 week reversibility increased when the number of insults decreased.[29] Furthermore, in elderly cancer patients, the most frequent and reversible aetiology is drug-induced delirium resulting from opioids and other psychoactive medications.[30]

Treatment of any physical cause underlying the delirium should be started promptly. General principles include

Table 109.4 Main predisposing and precipitating factors of delirium.

Predisposing factors	Precipitating factors
Demographic characteristics	*Drugs*
Age 65 years or older	Sedative hypnotics
Male gender	Narcotics
	Anticholinergic drugs
Cognitive status	Polypharmacy
Dementia	Alcohol or drug withdrawal
Cognitive impairment	
History of delirium	*Primary neurological diseases*
Depression	Stroke
	Intracranial bleeding
Functional status	Meningitis or encephalitis
Functional dependence	
Immobility	*Intercurrent illnesses*
Low level of activity	Infections
	Iatrogenic complications
History of falls	Severe acute illness (hypoxia, fever, anaemia, dehydration)
Sensory impairment	
Visual impairment	*Surgery*
Hearing impairment	
Decreased oral intake	*Environmental*
Dehydration	Hospitalization
Malnutrition	Use of physical restraints
	Use of urinary catheter
Drugs	Use of multiple procedures
Treatment with multiple psychoactive drugs	Pain
	Emotional stress
Polypharmacy	
Alcohol abuse	

Adapted from Inouye.[27]

nursing in bright conditions with familiar staff members. If wandering is problematic, 'one-to-one' nursing management may have to be implemented for the patient's safety. The most effective supportive treatment is haloperidol with an initial dose of 0.5 mg twice daily.[31] Short-term use of antipsychotic agents is advised as these agents have been associated with a higher risk of mortality and possibly stroke when used in patients with dementia.[32] Benzodiazepines have a more rapid onset of action than the psychotics, but they can worsen confusion and sedation.

Structural emergencies

Structural emergencies include airway, bowel and urinary obstructions and pathological fractures.

Airway obstruction

Airway obstruction in elderly cancer patients may have different causes, from swallowing disorders to tumours involving the upper (hypopharynx, larynx and trachea to carina) or lower airway.

Clinical differentiation between upper and lower airway obstructions can be difficult because both can cause cough, wheezing, dyspnoea, infection, respiratory failure and death.

A rapid evaluation must ensure that no foreign body is inhaled. In the case of an upper airway tumour mass, emergency visualization of the larynx by an otolaryngologist or anaesthesiologist must be performed in order to pass an endotracheal tube, based mainly on the condition and life expectancy of the patient. Treatment associates low tracheotomy with placement of a long tracheostomy tube, adjunctive therapy such as corticosteroids (to reduce oedema), humidified oxygen and bronchodilators and definitive therapy, based on underlying disease (chemotherapy for sensitive cancers, radiotherapy, surgery, endoscopic laser and stenting for the others). Similarly, endobronchial obstruction is treated with radiation therapy, surgical or endoscopic procedures.

Bowel obstruction

Lack of intestinal emission is frequent in the elderly and a clinical distinction must be made between constipation and intestinal occlusion. Faecal impaction must be kept in mind, especially in bedridden patients. Cancer-related obstruction may have mechanical and/or functional causes. Within the lumen, obstruction can occur owing to annular or polypoïd lesions. Externally, malignant or surgical adhesions, radiotherapy-related fibrosis and omental or mesenteric tumours may result in obstruction. Finally, tumour infiltration to the bowel muscle or mesentery may cause motility disorders (pseudo-obstruction).

Intestinal colic, abdominal pain and vomiting are associated with anorexia, intermittent borborygmi and abdominal distension. Significant sequelae of bowel obstruction include potential life-threatening perforation, intravascular volume depletion and sepsis.

Based on a threshold of 75 years, preoperative complication and emergency surgery rates are more common in elderly patients. Whereas postoperative surgical morbidity rates are similar to those observed in younger patients, postoperative non-surgical morbidity is higher in the elderly group, which influences postoperative mortality.[33] When a surgical procedure is contraindicated, alternative therapy includes the use of a nasogastric tube, analgesics, centrally acting antiemetics (haloperidol, prochlorperazine), antisecretory agents (octreotide rather than anticholinergic agents) and corticosteroids (tapered to the minimum effective dose that controls symptoms).

Urinary obstruction

Obstruction of the upper urinary tract, primarily the ureters, is common in a variety of cancers. When compression is bilateral either simultaneously or sequentially, early intervention may prevent life-threatening complications such as anuria and renal failure. This may be caused by obstruction to bladder outflow or to one or both ureters and occurs commonly in genitourinary malignancy. Ureteric obstruction may be produced by intraluminal, intramural or extramural tumours. Retroperitoneal fibrosis and stricture caused by radiotherapy, chemotherapy or surgery may also lead to progressive upper tract obstruction.

Patients commonly present with the insidious onset of uraemia and reduced urine output. Pain is rarely a feature, unless there is acute obstruction of a ureter. If there is concomitant infection, then urosepsis may intervene unless prompt drainage is performed using percutaneous nephrostomy or retrograde stenting of the ureter. Procedure choice depends on life expectancy, comorbidity and patient preference.

Pathological fractures

Fractures of weight-bearing bones are common in the elderly due to osteopenia. This tendency is enhanced in patients with cancer due to local metastasis or to tumour-enhanced osteopenia. Bone pain is the most common presenting feature of either pathological fracture or of impending pathological fracture, but it is not absolutely essential for the diagnosis. Around 50% of events are due to metastasis from breast cancer and the commonest site for pathological fracture is the femur.

Whether fractures are displaced, non-displaced, impending in weight-bearing bones or in non-weight-bearing bones are all important factors for management decisions. These

tumour-related factors, along with patient-related factors, such as performance status, comorbidity, previous mobility and geriatric evaluation, need to be assessed. For example, surgical intervention for fractures in non-weight-bearing bones may be considered worthwhile when survival is expected to be at least 3 months, whereas for fractures in weight-bearing bones it should be considered even with a life expectancy limited to 1 month. Pain relief may be an objective as important as stability or mobility. Radiation therapy is a highly effective modality for treating painful bones metastases. Where a fracture has occurred, surgical intervention should always be considered in the first instance, unless it involves regions not amenable to orthopaedic intervention such as ribs, scapula or pelvis. In these cases, radiotherapy can provide pain relief in up to 80% of patients, while promoting bone healing. For long bone fractures, rigid immobilization with internal fixation should be performed prior to irradiation, in order to give the lesion the best chance of healing.

Acute pain emergencies

Acute cancer pain in the elderly population is an increasingly common clinical situation. Previous studies indicate a high prevalence rate (between 25 and 40% of elderly patients with cancer experience daily pain)[34] and poor management of cancer pain in the elderly. Pain is often considered as an expected concomitant of ageing and older patients are considered more sensitive to opioids. Furthermore, no physiological changes in pain perception in the elderly have been demonstrated. In fact, the elderly may be less likely to complain of pain than younger people.[35] However, the assessment of pain in elderly individuals with cancer may pose significant and specific challenges, notably in emergency. The presence of multiple concurrent medical problems, the increased likelihood of cognitive and sensory impairment and the presence of depression may all contribute to underestimation of pain.

In practice, because of the many variables in pain, it is essential to have a standard approach to assessment, notably in elderly cancer patients. This includes

- taking an accurate pain history
- using an assessment tool
- standard clinical examination
- appropriate laboratory and radiological investigation.

Pain assessment tools help in understanding the patient's pain and facilitate monitoring of the effects of analgesics and other interventions. Furthermore, not all tools for pain assessment are equally reliable in the elderly. Numerical rating scales, pictorial pain scales and verbal descriptor scales are more reliable than visual analogue scales.[36]

The most important is to use the same scale during follow-up evaluation, ensuring reproducibility and easy comparison. Moreover, the key to performing pain assessment in the cognitively impaired patient is to assess pain frequently (because of poor recall) and recognize changes. Behavioural cues, such as a change in cognitive level or appearance, increased agitation or change in respiratory status, may indicate pain.[37]

Subsequently, physical examination should be aimed at identifying causes of pain, for example, tenderness from bone metastases, evidence of bowel obstruction and neurological dysfunction as a pointer to neuropathic pain or patterns suggestive of cancer pain syndromes. Investigation may be necessary to confirm areas of suspected disease.

Finally, the general principles in managing acute cancer pain in the elderly are similar to those in the general population, but with a greater degree of caution. Effective pain management may be achieved by any one of the following modalities: delay tumour progression (chemotherapy, radiotherapy, . . .), palliative surgery (spinal cord decompression, . . .) and analgesics and adjuvant analgesic drugs. Frequently a combination is necessary.

However, analgesic pain management in elderly patients requires taking into consideration the physiological and pharmacokinetic changes that occur in the geriatric population, the phenomenon of poly-pharmacy, which is common in the elderly, and the treatment goals. Elderly patients are potentially more likely to be affected by opioid toxicity because of the physiological changes associated with ageing. Nevertheless, appropriate dosage and administration may limit these risks. Cancer patients with acute pain not responding to increased opioid doses because they develop adverse effects before achieving acceptable analgesia may be switched to alternative opioids. Adjuvant analgesics, including antidepressants, antiepileptics, corticosteroids and bisphosphonates, may help in the treatment of certain types of pain. On the other hand, the elderly are at increased risk of developing toxicity from non-steroidal anti-inflammatory drugs (NSAIDs) and the overall safety of these drugs in frail elderly patients should be considered.

Finally, with an appropriate and careful approach, it should be possible to soothe acute cancer pain in most elderly patients. Then, the goal of optimal pain management is to maximize quality of life and independence.[38]

The role of geriatric evaluation in the prediction of oncological emergencies

The prevalence of cancers increases with age, half of them being diagnosed after 70 years of age, which implies new healthcare management challenges.[39,40] Both the US National Comprehensive Cancer Network (NCCN) and the International Society of Geriatric Oncology (SIOG)[41] recommend some form of pretreatment geriatric assessment to identify older adults fit enough to undergo standard treatment and those who need adjusted treatment.[42,43]

However, a geriatric assessment is time consuming and the benefits have not yet been demonstrated,[44] and traditional geriatric assessment may not be a sensitive tool to predict treatment toxicity in well-functioning and autonomous older adults. A more sensitive way to characterize health and functional status is to use the concept of frailty.[45] Frailty represents a state of reduced homeostasis and resistance to stress that leads, in turn, to increased vulnerability and risk of adverse outcome. Measures of frailty proposed by Fried *et al*. include weakness, poor endurance, reduced physical activity, slow walking speed and unintentional weight loss during the preceding year.[46] The concept of frailty is intended to identify older persons at risk of adverse outcome, with the aim of preventing or delaying the occurrence of adverse outcome. In a prospective pilot study, low grip strength and poor cognitive functioning were associated with treatment-related toxicity in unadjusted analyses.[45] Furthermore, the only frailty marker to be a statistically significant predictor of severe toxicity in the adjusted analyses was low grip strength, shown to predict disability in the elderly and mortality. Bohannon suggested that grip strength should be considered as a vital sign for older person.[47]

Moreover, among newly diagnosed older cancer patients, suspicion of cognitive impairment is associated with emergency department visits.[48] According to Kurtz *et al*., lower physical functioning increases the risk of emergency department visits during the active treatment and the follow-up period.[49,50] However, many patients were included after the start of cancer treatment, hence it is unclear whether the low physical functioning was treatment induced or due to the pre-existing comorbid conditions.

Finally, in older patients, cancer treatments, especially chemotherapy, are considered strong stressors that reveal patients with sufficient functional reserve to regain stable homeostasis. Frailty markers may add important information to that obtained using traditional geriatric tools such as instrumental activities of daily living and basic activities of daily living in detecting potential vulnerability. However, further longitudinal studies are needed to investigate the usefulness of frailty markers in predicting the risk of oncological emergencies.

Conclusion

Cancer is predominantly a disease of the elderly. More than 60% of all incident cases of cancer and more than 70% of all deaths from malignant tumours occur in older individuals. Elderly patients with malignancies are subject to developing a unique set of complications that require urgent evaluation and treatment. Geriatricians must be able to recognize these conditions and to institute appropriate therapy. With timely intervention, many of these elderly cancer patients can return to their previous level of function and independence. Therefore, it is important that geriatric physician have a sound knowledge of the most common oncological emergencies.

Key points

- The majority of deaths in those with malignant tumours occur in older patients.
- Physicians should be familiar with oncological emergencies, as failure to implement immediate and appropriate treatment may result in significant morbidity or death.
- Common problems include haematological emergencies, infections, neurological and metabolic derangements and tumour lysis syndrome.

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CHAPTER 110

Breast cancer

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The presentation

Diagnosis of breast cancer in the elderly is made by the discovery of a lump in 60–80% women. Since screening is applied less rigorously to elderly patients, the majority of women present with a palpable lump. Several studies have revealed that the stage at presentation is more advanced in elderly women.[1,2] A patient care evaluation survey was conducted by the Commission on Cancer of the American College of Surgeons for 1983 and 1990.[3] They surveyed all States of USA, including Puerto Rico, and Canada and studied 17 029 women in 1983 and 24 004 women in 1990. Some 20% women in 1983 and 23% in 1990 were 75 years of age or older. The survey included 2000 hospitals (25 patients from each). The percentage of cancers detected by physicians' examination decreased in the younger group from 27% in 1983 to 21% in 1990, whereas in the elderly the corresponding figures were 41 and 34%, respectively.

Veronesi's group in Milan reported various features of presentation and choice of therapy in the elderly.[4] They studied 2999 postmenopausal patients referred for surgery at the European Institute of Oncology, Milan, from 1997 to 2002. The patients were grouped according to age: young postmenopausal (YPM, age 50–64 years, $n = 2052$), older postmenopausal (OPM, age 65–74 years, $n = 801$) and elderly postmenopausal (EPM, age $\geq$75 years, $n = 146$). EPM patients had larger tumours compared with YPM patients (pT4: 6.7 versus 2.4%) and more nodal involvement (lymph node positivity: 62.5 versus 51.3%). EPM patients showed a higher degree of estrogen and progesterone receptor expression, less peritumoral vascular invasion and less human epidermal growth factor receptor-2 (HER-2)/*neu* expression than YPM patients. Although comorbidities were more often recorded for elderly patients (72% EPM versus 45% YPM), this did not influence surgical choices, which were similar across groups (breast conservation: 73.9, 76.9 and 72.9%, respectively). No systemic therapy was recommended for 19.1% of the EPM group compared with 5.4 and 4.7% of the two other groups. A recent epidemiological study in The Netherlands[5] of 127 805 adult female patients with their first primary breast cancer diagnosed between 1995 and 2005 showed that elderly breast cancer patients were diagnosed with a higher stage of disease. Elderly patients underwent less surgery (99.2 versus 41.2%), received hormonal treatment as monotherapy more frequently (0.8 versus 47.3%) and less adjuvant systemic treatment (79 versus 53%).

In women over 70 years of age, estrogen receptor-positive tumours are more common, range 69–95%, compared with all tumours, range 53–72%.[3]

Pathologically infiltrating ductal carcinoma accounts for 77–85% of all tumours in elderly women compared with 68% in younger women. There is an increase in the proportion of papillary and mucinous carcinoma with advancing age. Whereas the number of lobular carcinoma *in situ*, comedo, medullary and inflammatory carcinoma decreases with advancing age, the prevalence of ductal carcinoma *in situ* (DCIS) increases until 75 years, after which it declines.[6,7]

In summary, elderly women generally present with large palpable estrogen receptor-positive, infiltrating ductal carcinoma with a positive lymph node.[5,7]

Stage of presentation

There is generally a delay in the diagnosis of breast cancer in elderly women. In a study by Berg and Robbins,[8] the diagnosis was delayed by more than 6 months in 28% of women under 70 years of age compared with 42% in women above the age of 70 years. Similarly, Devitt[9] observed a delay of more than 6 months in diagnosis in 35% of women above the age of 70 years compared to 28% below that age. The tumour is generally advanced in the elderly group, as shown in Table 110.1.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 110.1 TNM stage (%) with age at presentation.

Age (years)	Stage				Ref.
	I	II	III	IV	
>80	52	18	6	24	10
>80	25	49	15	10	11
>75	53	22	12	13	12

Variation in care and undertreatment in the elderly

There is growing evidence that there is significant variation in standard care of breast cancer in the elderly and that elderly patients often receive suboptimal treatment. Monica Morrow, in a review on treatment in the elderly, noted that screening by physical examination and mammography is underutilized for the older women.[13] Since mastectomy offers excellent local control and has only less than 1% operative mortality in women above 65 years of age, it should be offered to more (suitable) patients. She further pointed out that failure to use adjuvant therapy when indicated is one of the most frequent problems in management of elderly.[13]

Pattern of care of elderly women is different from that offered to younger patients. In the study by the Commission on Cancer of the American College of Surgeons for 1983 and 1990,[3] in 1983, 23% of older women received total or partial mastectomy without axillary dissection compared with 8% of younger females. In 1990, the rate of total or partial mastectomy without nodal dissection was 20.6% in older women and 10% in younger women. The use of reconstruction was limited in the older women. The percentage of elderly females receiving reconstruction was 1.2% in 1983 and 1.3% in 1990. The operative mortality rates were higher in the older age-group (2.9% in 1983 and 1.5% in 1990). Radiotherapy was used less frequently in the older group in both study years.

In an editorial in the *Journal of Clinical Oncology*, Rebecca Silliman chided clinicians for not offering definitive treatment to elderly women with breast cancer.[14] Although breast cancer-specific mortality has declined among women younger than 70 years, it is either stable in those aged 70–79 years or increased in women above 65 years of age. This proportion is likely to grow, as older age is the most important risk factor for breast cancer and gains in life expectancy will result in more women being at risk for longer periods. Currently, the average life expectancy of a 75-year-old woman is 12 years (17 years if she is healthy) and that of an 85-year-old is 6 years (9 years if she is healthy). Owing to paucity of good evidence-based data, there is considerable controversy about what constitutes appropriate care for older women. More than one-quarter (27%) of breast cancer deaths in 2001 in the USA were in the age group of 80 years and older. Although the patient's health status, patient and family preferences and support and patient–physician interactions explain in part age-related treatment variations, age alone remains an independent risk factor for less than definitive breast cancer care.

In a cohort of 407 octogenarian women in Canton of Geneva, Switzerland, Bouchardy *et al*.[15] addressed the relationship between undertreatment and breast cancer mortality. They used tumour registry data, including sociodemographic data, comorbidity, tumour and treatment characteristics and the cause of death. The main problem that they noted in analysing these data was the issue of missing information – 20% for comorbidity, 49% for tumour grade and 74% for estrogen receptor (ER) status. Because of loss of data on these important prognostic factors, there was a problem in multivariate analysis and incomplete control of confounding, decreasing the statistical power and precision. Both mastectomy plus adjuvant therapy and breast-conserving surgery plus adjuvant therapy appear to protect against death from causes other than breast cancer, suggesting residual confounding either because comorbidity was not well measured or because undertreatment of breast cancer is associated with undertreatment of other medical conditions. This cohort of Swiss women differed from women presenting elsewhere. The average tumour size in this group was 30 mm, only 22% presented in Stage I, 22% received no therapy and 32% received tamoxifen alone. Despite the limitations of this study, it highlights the link between undertreatment and high rates of breast cancer recurrence and mortality.

A recent retrospective cohort study involving case-note review based on the North Western Cancer Registry database of women aged ≥65 years resident in Greater Manchester with invasive breast cancer registered over a 1 year period ($n = 480$) showed that even after adjusting for tumour characteristics associated with age by logistic regression analyses, older women were less likely to receive standard management than younger women for all indicators investigated.[16] Compared with women aged 65–69 years, women aged ≥80 years with operable (Stage I–IIIa) breast cancer have increased odds of not receiving triple assessment [odds ratio (OR) = 5.5, 95% confidence interval (CI), 2.1–14.5], not receiving primary surgery (OR = 43.0; 95% CI, 9.7–191.3), not undergoing axillary node surgery (OR = 27.6; 95% CI, 5.6–135.9) and not undergoing tests for steroid receptors (OR = 3.0; 95% CI, 1.7–5.5). Women aged 75–79 years have increased odds of not receiving radiotherapy (RT) following breast-conserving surgery compared to women aged 65–69 years (OR = 11.0; 95% CI, 2.0–61.6). These results demonstrate that older women in the UK are less likely to receive standard management for breast cancer

compared with younger women and this disparity cannot be explained by differences in tumour characteristics.

In a recent German clinical cohort study, 1922 women aged >50 years with histologically confirmed invasive breast cancer treated at the University of Ulm from 1992 to 2005 were enrolled.[17] Adherence to guidelines and effects on overall survival (OAS) and disease-free survival (DFS) for women aged >70 years were compared with those for younger women (aged 50–69 years). The study found that women aged >70 years less often received recommended breast-conserving therapy (70–79 years, 74–83%; >79 years, 54%) than women aged <69 years (93%). Non-adherence to the guidelines on RT (<70 years, 9%; 70–79 years, 14–27%; >79 years, 60%) and chemotherapy (<70 years, 33%; 70–79 years, 54–77%; >79 years, 98%) increased with age. Omission of RT significantly decreased OAS [<69 years, hazard ratio (HR) = 3.29; $p < 0.0001$; >70 years, HR = 1.89; $p = 0.0005$] and DFS (<69 years, HR = 3.45; $p < 0.0001$; >70 years, HR = 2.14; $p < 0.0001$). OAS and DFS did not differ significantly for adherence to surgery, chemotherapy or endocrine therapy. This study showed that substandard treatment increases considerably with age and omission of RT had the greatest impact on OAS and DFS in the elderly population.

Women suffering from heart disease, obstructive airway disease, stroke or other major incapacitating illnesses receive inadequate diagnostic and therapeutic attention. One study found that the main cause of under treatment in the over-65 age group patients was cited as prohibitive associated medical conditions.[18]

Nicolucci *et al*.[19] analysed the data on 1724 women treated in 63 general hospitals in Italy. A comorbidity index was computed from individual disease value (IDV) and functional status (FS). IDV summates the severity and presence of specific complications for each disease suffered on a scale of 0–3, with 0 = full recovery and 3 = life-threatening disease. FS from signs and symptoms of 12 system categories evaluated the impact of all conditions, whether diagnosed or not, on patients' health status. The study showed higher proportions of inadequate diagnosis and therapy in the elderly group. The quality of care was assessed by a score based on observed degree of compliance with standard care. The median value of overall diagnostic and staging score was 60%. About one-third of surgical operations were inappropriate; 24% of cases with Stage I–II disease had unnecessary Halsted mastectomy and breast conservation in smaller tumours of ≤2 cm was underutilized. The presence of one or more coexisting diseases was associated with failure to undergo axillary dissection and lower utilization of conservative surgery.

Alvan Feinstein, a famous clinical epidemiologist from Yale, has said that the failure to classify and analyse comorbid disease has led to many difficulties in medical statistics.[20] There are four reasons for measuring comorbidity correctly: (1) to be able to correct for confounding, thus improving the internal validity of the study, (2) to be able to identify effect modification, (3) the desire to use comorbidity as a predictor of outcome and (4) to construct a comprehensive single comorbid scale that is valid, to improve the statistical efficiency. de Groot *et al*.[21] reviewed various comorbidity indices. The following indices have been applied for patients with breast cancer. The Charlson index is the most extensively studied method and includes 19 diseases which are weighted on the basis of strength of association with mortality. The disease count index simply counts the coexisting diseases but lacks a consistent definition and weighting for different diseases. The Kaplan index uses the type and severity of comorbid condition, for example, types are classified vascular (hypertension, cardiac disease, peripheral vascular disease) and non-vascular (lung, liver, bone and renal disease). It has good predictive validity for mortality. It may be worthwhile for all the agencies involved in breast cancer research to adopt one of the above indices and record it prospectively.

Screening in the elderly

Currently, all women in the UK between ages 50 and 70 years are offered breast cancer screening, which is saving ~1400 lives every year (2009 NHSBSP Annual Review). Although previously women between 65 and 70 years of age were eligible, they were not offered screening routinely. Extended age pilot schemes are now under way in which the age of inclusion includes women between 47 and 73 years of age. In 2007–08, 16 449 new cancers were detected under this programme. In England, in 2008–09 just under 1.8 million women (aged 45 years and over) were screened within the programme, an increase of 3.5% over 2007–08. The previous 10 years saw the programme grow by 43.9% from 1.2 million in 1998–99. There were 14 166 cases of cancer diagnosed in women screened aged 45 years and over, similar to the previous year (14 110) and nearly double the number in 1998–99 (7561). Of all cancers diagnosed, 11 212 (79.1%) were invasive and of these 5850 (52.2%) were 15 mm or less in size, which could not have been detected by clinical examination alone.

It has been observed that with increasing age the number of screening-detected cancers detected increases (Table 110.2).

In order to enhance the rate of breast examination by doctors of women above 65 years of age and to increase compliance with mammography, Herman *et al*.[22] conducted a randomized clinical trial (RCT) at the Metro Health Medical Center, Cleveland, OH. All house staff in Internal Medicine were asked to complete a questionnaire about their attitude towards prevention of breast cancer in elderly people after providing some basic information (monograph and a lecture). In one arm (controls), no specific interventions were offered. In the next group (education),

Table 110.2 Result of UK breast cancer screening – 2004 review NHS Breast Cancer Screening Programme in the UK, 2005.

Age (years)	Cancer detected per 1000 women screened
50–64	7.6
65–69	20.6

Table 110.3 Rates of examination and mammography by intervention.

Group	Breast examination (%)	Mammography (%)
Control ($n = 192$)	18	18
Education ($n = 183$)	22	31
Prevention ($n = 165$)	32	36

nurses provided educational leaflets to patients attending the clinics. In the third group (prevention), nurses filled the request forms and facilitated women to undergo mammography. The results are given in Table 110.3. The study suggested that encouragement and education of older women by motivated doctors and nurses improves compliance.

Chen *et al*.[23] reported the mortality rate of women aged 65–74 years screened in the Swedish two-county trial – 77 080 women were randomized to undergo screening every 33 months and 55 985 women served as controls. Of the screened group, 21 925 were in the age group 65–74. In the control arm, 15 344 women belonged to the age group 65–74 years. The relative breast cancer mortality in the screened group was 0.68, demonstrating a survival advantage in the elderly population.

Risk factors in the elderly

With advancing age, the risk of developing breast cancer rises. In a cohort of National Surgical Adjuvant Breast and Bowel Project's breast cancer prevention trial in the USA, the presence of non-proliferative lower category benign breast disease (LCBBD) was found to increase the risk of invasive breast cancer. The overall relative risk (RR) of breast cancer was 1.6 for LCBBD compared with women without any LCBBD. This risk increased to 1.95 (95% CI, 1.29–2.93) among women aged 50 years and over.[24]

Hormone replacement therapy (HRT) has been identified as a risk factor for breast cancer. The impact of HRT on the incidence and death due to breast cancer in the UK was assessed through a study of over 1 million women.[25] In this prospective cohort of 1 084 110 women aged 50–64, current users of HRT were found to have a higher risk of developing breast cancer than non-users (RR = 1.66; 95% CI, 1.58–1.75). The risk was highest for combined estrogen + progestogen (RR = 2; 95% CI, 1.88–2.12) than for estrogen alone (RR = 1.3; 95% CI, 1.2–1.4) and for tibolone (RR = 1.45; 95% CI, 1.25–1.68) compared with those who never used this treatment. There was a dose–response relationship of increasing risk of cancer with increasing duration of HRT usage, the highest being with combined estrogen + progestogen used for 10 years or more (RR = 2.31; 95% CI, 2.08–2.56).

The Danish Nurses Cohort study[26] provided data on 10 874 nurses (aged 45 years and above). Of these, 244 women developed breast cancer. After adjusting for confounding, increased risk was found with current use of estrogens (RR = 1.96; 95% CI, 1.16–3.35), for combined use of estrogen + progesterone (RR = 2.7; 95% CI, 1.96–3.73), for current use of tibolone (RR = 4.27; 95% CI, 1.74–10.51), compared with never used HRT. In current users of combined HRT with progestins, continuous combined use has a higher risk (RR = 4.16; 95% CI, 2.56–6.75) than cyclical combined use (RR = 1.94; 95% CI, 1.26–3).

Natural history of breast cancer in the elderly

It has long been thought that breast cancer in the elderly is rather indolent and a biologically less aggressive disease. Singh *et al*.[27] studied the metastatic proclivity as indicated by the virulence (defined as the rate of appearance of distant metastasis) and metastagenecity (defined as the ultimate likelihood of developing distant metastasis). They examined 2136 women who underwent mastectomy without systemic adjuvant therapy at the University of Chicago Hospitals between 1927 and 1987. The median follow-up period was 12 years. Distant disease-free survival (DDFS) was determined and virulence (V) and metastagenecity (M) were obtained from log-linear plots of DDFS. No significant difference was observed between size of primary tumour in the age groups <40, 40–70 and >70 years. Significantly, fewer women above 70 years of age presented with positive nodes. In women with negative nodes, the DDFS was higher among those aged 40–70 years, compared with those aged >70 years. However, no significant difference was observed in the DDFS in the node-positive group in any of the age categories. The 10 year DDFS for age 40–70 years was 33% and for women aged >70 years it was 38%. Among the node-negative women, V was 3% per year for age 40–70 years and also for age >70 years and M was 0.2 for age 40–70 years and 0.35 for age >70 years. In women with positive nodes, both V (11 versus 10% per year) and M (0.7 versus 0.65) were similar in both age groups. It was concluded that there was no evidence that breast cancer was more indolent in the elderly. Therefore, similar diagnostic and therapeutic efforts should be made in elderly as in

younger women, the only modification being made on the basis of comorbidity.

Treatment of operable disease

The optimum treatment of breast cancer in the elderly is not yet well established. It is reasonable to apply the principles of therapy largely learned from studies in younger cohorts of women, namely breast conservation therapy (BCT) and sentinel lymph node biopsy (SLNB)/axillary clearance for smaller lesions, mastectomy for larger tumours, tamoxifen or aromatase inhibitors for ER-positive lesions and chemotherapy for node-positive or >1 cm tumours and RT for locally advanced lesions. SLNB is now the operative technique of choice for intraoperative staging of the axilla as established by major RCTs. Axillary clearance should now only be reserved for patients who are found to have biopsy- or fine-needle cytology-proven node-positive disease preoperatively or proven sentinel node metastases following an SLNB.

Unlike the treatment of younger women, which is based on sound high-level evidence from meta-analyses of large RCTs, the therapy for the elderly is not evidence based, as there is a paucity of large RCTs. Women over 65 years of age have been excluded from many trials. In order to fill this lacuna in knowledge, two European Organization for Research and Treatment of Cancer (EORTC) trials were set up. In the UK, a CRC trial and a trial at Nottingham were conducted to answer the question of what would be the best therapy for the elderly. Moreover, a decision analysis has also been performed by Punglia *et al*.[28] Truong *et al*.[29] reported an overview of the literature on BCT in elderly women with early breast cancer. They found a paucity of prospective data and numerous retrospective series of diverse treatments with conflicting results. Their observation supports BCT + postoperative RT as the standard of care for the elderly.

As mentioned previously, treatment of elderly patients with breast cancer is limited by the lack of evidence-based medicine due to the exclusion of elderly patients from clinical studies and the difficulty of decision-making in an elderly population comprising subjects with heterogeneous health backgrounds. Among cooperative group clinical trials sponsored by the National Cancer Institute for early-stage breast cancer, women aged 65 years and above constitute only 18% of participants, although they constitute 49% of the eligible pool of all newly diagnosed cases. Physicians have been incriminated as the key barrier to enrolling older women in trials.[30] The difficulty of recruitment into clinical trials aimed at elderly patients is also a major issue. A recent trial looking at the efficacy of anastrozole with or without surgery for older women with breast cancer (ESTEeM) in the UK was suspended after failing to recruit suitable patients.

Crowe *et al*.[31] reported the outcome of modified radical mastectomy (MRM) in a group of 1353 women (age range 22–75 years). The HR for death was similar in all the three age-groups (<45, 46–65 and >65 years), demonstrating that older women achieve similar results to younger ones, provided that they are treated adequately.

The Cancer Research UK Breast Cancer Trial Group[32] conducted an RCT for women over 70 years of age with operable breast cancer. Of 455 patients, from 27 hospitals in the UK, 225 were randomized to surgery + tamoxifen and 230 to receive tamoxifen alone. The analysis was based on a median follow-up of 12 years. The local control was better achieved when surgery was combined with tamoxifen. Fifty-seven patients randomized to surgery and 141 to tamoxifen alone progressed. The HR for local progression for tamoxifen compared with mastectomy was 17.24 (95% CI, 6.4–47.6) and for tamoxifen compared with BCT it was 5.99 (95% CI, 4.12–8.7). The risk of local progression was greater in the BCT arm compared with mastectomy (HR = 2.98; 95% CI, 1.06–8.39). The 5 year risk of local progression was 8% after mastectomy, 18% after breast conservation and 64% in women who had tamoxifen alone. The 10 year survival was 37.7% for surgery + tamoxifen and 28.8% for tamoxifen alone. Primary tamoxifen therapy is inferior to mastectomy and breast-conserving surgery in achieving local control. Among patients randomized to surgery + tamoxifen, the risk of local progression was greater in those who had breast conservation than in those who had a mastectomy.[32]

A Cochrane review noted that data based on an estimated 869 deaths in 1571 women were unable to show a statistically significant difference in favour of either surgery or primary endocrine therapy in respect of overall survival.[33] However, there was a statistically significant difference in terms of progression-free survival, which favoured surgery with or without endocrine therapy. The HRs for overall survival were 0.98 (95% CI, 0.74–1.30; $p = 0.9$) for surgery alone versus primary endocrine therapy and 0.86 (95% CI, 0.73–1.00; $p = 0.06$) for surgery plus endocrine therapy versus primary endocrine therapy. The HRs for progression-free survival were 0.55 (95% CI, 0.39–0.77; $p = 0.0006$) for surgery alone versus primary endocrine therapy and 0.65 (95% CI, 0.53–0.81; $p = 0.0001$) for surgery plus endocrine therapy versus primary endocrine therapy (each comparison based on only one trial). It was concluded that primary endocrine therapy should only be offered to women with ER-positive tumours who are unfit for or who refuse surgery. In a cohort of women with significant comorbid disease and ER-positive tumours, it is possible that primary endocrine therapy may be a superior option to surgery. Trials are needed to evaluate the clinical effectiveness of aromatase inhibitors as primary therapy for an infirm older population with ER-positive tumours.

Role of radiotherapy

In a study by the University of Pennsylvania of 558 women aged ≥50 years who had been treated with breast conservation and RT for Stage I and II breast cancer, there were 173 women who were aged ≥65 years. Treatment included complete gross excision of tumour, pathological axillary lymph node staging and breast irradiation. Women aged ≥65 years and those between 50 and 64 years were found to have large T2 lesions (43 versus 34%; $p = 0.05$) and ER negativity (9 versus 16%; $p = 0.13$). The proportions of axillary node positivity (24%) and also the mortality rates due to breast cancer at 10 years (13%) were similar in elderly patients and those in the 50–64 year age group. The overall survival at 10 years (77 versus 85%; $p = 0.14$), local failure (13 versus 12%; $p = 0.6$) and freedom from distant metastasis (83 versus 78%; $p = 0.45$) were similar. The study revealed that breast cancer in the elderly is not an indolent disease and has many aggressive prognostic factors. Moreover, breast-conserving surgery and RT achieves good local control and a survival comparable to that in women aged <65 years.[34]

It is thought by some that in a selected group of elderly women, RT could be avoided. Gruenberger *et al*.[35] at the University of Vienna evaluated the need for RT in a retrospective review of 356 women aged >60 years, treated by quadrantectomy + axillary dissection followed or not followed by adjuvant radiation. Among node-negative, ER-positive cases, there was no benefit of RT as the locoregional recurrence (LR) rate was 3% with or without radiation. In this subgroup (ER-positive, node-negative women), adjuvant tamoxifen reduced the LR rate to 2% with or without radiation. The authors suggested that elderly women aged ≥60 years with a T1, ER-positive, node-negative tumour may be spared the toxicity of RT when treated by conservation surgery, axillary dissection and tamoxifen.

The instigator of the Milan trials of breast conservation, Professor Umberto Veronesi of the Milan Institute has been a great proponent of breast conservation. He initially developed the technique of quadrantectomy plus radiotherapy (QUART) and later reduced the extent of resection to only lumpectomy. The results of the Milan trials were published in a meta-analysis of data from 1973 patients treated in three consecutive randomized trials by four different radiosurgical procedures: Halsted mastectomy, QUART, lumpectomy plus RT and quadrantectomy without RT).[36] The median follow-up for all patients was 82 months. The annual rates of local recurrence were 0.2 for patients treated with Halsted mastectomy, 0.46 for QUART, 2.45 for lumpectomy plus RT and 3.28 for quadrantectomy without RT. The local recurrences were much higher in women under 45 years of age than those over 55 years of age. The overall survival was identical in the four groups of patients. This study indicated that in elderly patients, lumpectomy plus RT is a satisfactory option. RT should be considered as standard treatment in fit patients, but there is some evidence that it can be omitted in certain selected cases.

Adjuvant endocrine therapy

Since the majority of tumours in postmenopausal women are ER positive, hormonal manipulation by anti-estrogen molecules or aromatase inhibitors is used with advantage in over 60% of cases. Tamoxifen has been the standard adjuvant endocrine therapy in women with breast cancer for more than 25 years. However, aromatase inhibitors including anastrazole and letrozole should now be considered as first-line therapy for all ER-positive breast cancers in postmenopausal women. Tamoxifen should only be used if an aromatase inhibitor is not tolerated or contraindicated. The recent NICE guideline (February 2009) for the management of early breast cancer also recommends the above strategy based on the results of large RCTs.

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was designed to compare the efficacy and safety of anastrozole (1 mg) with tamoxifen (20 mg), both given orally every day for 5 years, as adjuvant treatment for postmenopausal women with early-stage breast cancer. A proportional hazards model was used to assess the primary endpoint of disease-free survival and the secondary endpoints of time to recurrence, time to distant recurrence, incidence of new contralateral breast cancer, overall survival and death with or without recurrence in all randomized patients (anastrozole $n = 3125$, tamoxifen $n = 3116$) and hormone receptor-positive patients (anastrozole $n = 2618$, tamoxifen $n = 2598$). After completion of treatment, data on fractures and serious adverse events in a masked fashion (safety population: anastrozole $n = 3092$, tamoxifen $n = 3094$) continued to be collected. Patients were followed up for a median of 120 months (range 0–145); there were 24 522 woman-years of follow-up in the anastrozole group and 23 950 woman-years in the tamoxifen group. The study found that in the full study population, there were significant improvements in the anastrozole group compared with the tamoxifen group for disease-free survival (HR 0.91; 95% CI, 0.83–0.99; $p = 0.04$), time to recurrence (HR 0.84; 95% CI, 0.75–0.93; $p = 0.001$) and time to distant recurrence (HR 0.87; 95% CI, 0.77–0.99; $p = 0.03$). For hormone-receptor-positive patients, the results were also significantly in favour of the anastrozole group for disease-free survival (HR 0.86; 95% CI, 0.78–0.95; $p = 0.003$), time to recurrence (HR 0.79; 95% CI, 0.70–0.89; $p = 0.0002$) and time to distant recurrence (HR 0.85; 95% CI, 0.73–0.98; $p = 0.02$). In hormone receptor-positive patients, absolute differences in time to recurrence between anastrozole and tamoxifen increased over time (2.7% at 5 years and 4.3% at 10 years) and recurrence rates remained significantly lower on anastrozole than tamoxifen after completion of treatment (HR 0.81; 95% CI, 0.67–0.98; $p = 0.03$), although the

carryover benefit was smaller after 8 years. There was weak evidence of fewer deaths after recurrence with anastrozole compared with tamoxifen treatment in the hormone receptor-positive subgroup (HR 0.87; 95% CI, 0.74–1.02; $p = 0.09$), but there was little difference in overall mortality (HR 0.95; 95% CI, 0.84–1.06; $p = 0.4$). Fractures were more frequent during active treatment in patients receiving anastrozole than those receiving tamoxifen (451 versus 351; OR 1.33; 95% CI, 1.15–1.55; $p < 0.0001$), but were similar in the post-treatment follow-up period (110 versus 112; OR 0.98; 95% CI, 0.74–1.30; $p = 0.9$). Treatment-related serious adverse events were less common in the anastrozole group than the tamoxifen group (223 anastrozole versus 369 tamoxifen; OR 0.57; 95% CI, 0.48–0.69; $p<0.0001$), but were similar after completion of treatment (66 versus 78; OR 0.84; 95% CI, 0.60–1.19; $p = 0.3$). No differences in non-breast cancer causes of death were apparent and the incidence of other cancers was similar between groups (425 versus 431) and continue to be higher with anastrozole for colorectal (66 versus 44) and lung cancer (51 versus 34) and lower for endometrial cancer (6 versus 24), melanoma (8 versus 19) and ovarian cancer (17 versus 28). No new safety concerns were reported. These data confirm the long-term superior efficacy and safety of anastrozole over tamoxifen as initial adjuvant therapy for postmenopausal women with hormone-sensitive early breast cancer.[37]

The Breast International Group (BIG) 1–98 study was a randomized, Phase III, double-blind trial that compared 5 years of treatment with various adjuvant endocrine therapy regimens in postmenopausal women with hormone receptor-positive breast cancer: letrozole, letrozole followed by tamoxifen, tamoxifen and tamoxifen followed by letrozole. The aromatase inhibitor letrozole is a more effective treatment for metastatic breast cancer and more effective in the neoadjuvant setting than tamoxifen. In this study, letrozole was compared with tamoxifen as adjuvant treatment for steroid hormone receptor-positive breast cancer in postmenopausal women. A total of 8010 women with data that could be assessed were enrolled, 4003 in the letrozole group and 4007 in the tamoxifen group. After a median follow-up of 25.8 months, 351 events had occurred in the letrozole group and 428 events in the tamoxifen group, with 5 year disease-free survival estimates of 84.0 and 81.4%, respectively. Compared with tamoxifen, letrozole significantly reduced the risk of an event ending a period of disease-free survival (HR 0.81; 95% CI, 0.70–0.93; $p = 0.003$), especially the risk of distant recurrence (HR 0.73; 95% CI, 0.60–0.88; $p = 0.001$). Thromboembolism, endometrial cancer and vaginal bleeding were more common in the tamoxifen group. Women given letrozole had a higher incidence of skeletal and cardiac events and of hypercholesterolaemia. The study group concluded that in postmenopausal women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease, especially at distant sites.[38]

Chemotherapy

Owing to concerns about excessive toxicity, there is a negative attitude towards chemotherapy in the elderly. Hence women above 65 years of age are not included in chemotherapy trials. In the National Institute of Health (NIH) consensus, chemotherapy is recommended only for women below 70 years of age.

Allocation to about 6 months of anthracycline-based polychemotherapy [e.g. with 5-fluorouracil, adiamycin and cytoxan (FAC) or 5-fluorouracil, epirubicin and cyclophosphamide (FEC)] reduces the annual breast cancer death rate by about 38% (SE 5) for women younger than 50 years of age when diagnosed and by about 20% (SE 4) for those aged 50–69 years when diagnosed, largely irrespective of the use of tamoxifen and of ER status, nodal status or other tumour characteristics. Such regimens are significantly ($2p = 0.0001$ for recurrence, $2p < 0.00001$ for breast cancer mortality) more effective than cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy. Few women of age $\geq$70 years entered these chemotherapy trials.[39]

Recently, taxanes have been tried in older women with good tolerance. Taxanes are considered a very effective drug in breast cancer and have been tried on weekly regimens. The toxicity of weekly therapy is much lower than that of 3 weekly courses. Since there is decreased clearance of both paclitaxel and docetaxel in the elderly, it seems safer to use lower doses of weekly regimens. A dose of paclitaxel of 80 mg m^{-2} per week and docetaxel 36 mg m^{-2} per week is usually well tolerated, with impressive response. Severe neutropenia, the dose-limiting toxicity of the 3 weekly regimen, is rare in weekly therapy.[40] In a Phase II study of weekly docetaxel 36 mg m^{-2} among 47 frail or elderly patients with metastatic breast cancer, a response rate of 30% with low toxicity was achieved.[41]

A recent review on the use of cytotoxic therapy noted that even in the in the fit elderly breast cancer patient, the use of chemotherapy has been tempered with concerns regarding age, physical function and comorbid illness.[42] In the appropriate patient with biologically aggressive disease, such as receptor-poor breast cancer, it is reasonable to consider combination chemotherapy as part of an adjuvant programme. If this approach is to be employed, the physician must also consider the patient's comorbid conditions and status of function in society as potential indicators of toxicity or lack of benefit. In this case, a formal geriatric assessment is of value. A Cancer and Leukemia Group B (CALGB) trial of monotherapy versus combination cytotoxic therapy as adjuvant treatment for localized breast cancer patients over 65 years of age determined that the combination approach is superior to single-agent therapy.

In an unplanned analysis of receptor-rich and receptor-poor tumours, the patients with receptor-poor tumours seemed to achieve the greatest benefit from combination cytotoxic therapy. Adjuvant chemotherapy can also be considered for patients with high-risk receptor-rich breast cancers. However, the use of chemotherapy in the elderly patient with breast cancer is largely based upon data emerging from trials in younger patients. Studies specifically for patients over 65 years of age are urgently needed in this population to provide evidence-based proof of the current approach.

Nowadays, trastuzumab (Herceptin) can be considered along with chemotherapy for patients with HER2+ breast cancer. There is currently no evidence of efficacy of adjuvant trastuzumab without concurrent use of chemotherapy. There is evidence to suggest that capecitabine, an oral chemotherapeutic drug, is safe and effective in elderly breast cancer patients.[43]

Treatment of advanced disease

Patients with locally advanced disease need evaluation by a combined breast care team and should be offered good local control by limited surgery and radiation followed by aromatase inhibitors and chemotherapy (preferably taxanes). Women presenting with a fungating or bleeding ulcer should not be denied the benefit of limited surgical ablation and coverage of the defect with a myocutaneous flap. Palliative haemostatic fractions of radiation may help arrest bleeding. Women with dissemination of cancer need systemic chemoendocrine administration until the level of tolerance and, later, tender loving care for the debility.

Prognostic factors in elderly breast cancer

Ian Fentiman, in an editorial in the *British Journal of Surgery*,[44] pointed out that 60% of deaths from breast cancer occurred in women of age 65 years and above because of late diagnosis and treatment.

The outcome for elderly patients and the post-treatment quality of life (QOL) has been studied by a number of groups. Age has been considered an important determinant of the type of treatment and hence the outcome. In the CRUK trial, age and tumour size were found to predict mortality independently.[32]

Data from six regional National Cancer Institute Surveillance Epidemiology End Result Cancer registries evaluated a population-based random sample of 1800 patients in the age group ≥55 years. About 73% of the women presented with Stage I and II breast cancer, 10% with Stage III and IV and 17% did not have stage assignment. Of the 1017 cases with Stage I and II node-negative disease, 95% of women received therapy in agreement with NIH consensus. Patients in older age groups were less likely to receive therapy according to the consensus statement. Women aged ≥70 years were significantly less likely to receive axillary lymph node dissection. Diabetes, renal failure, stroke, liver disease and history of smoking were significant predictors of early mortality in a statistical logistic regression model that included age and disease stage. The authors concluded that patient care decision-making occurs in the context of age and other comorbid conditions. Comorbidity in older patients results in smaller number of axillary dissections. As a result, information on axillary nodes is not available in many elderly patients. Breast cancer was the underlying cause of death in 51% and heart disease in 17%. The number of women receiving breast conservation therapy is also reduced and comorbidity also increases the risk of death from breast cancer.[45]

Quality of life issues

The impact of the diagnosis of breast cancer and the effect of different therapeutic modalities has been addressed by a number of authors. Kroenke *et al*.[46] of the Harvard School of Medicine and Harvard School of Public Health reported changes in physical and psychological functions before and after breast cancer by age at diagnosis. Of 122 969 women from the Nurses' Health Study (NHS) and NHS2 of age 29–71 years who responded to a pre- and postfunctional status assessment who were included, 1082 women were diagnosed with breast cancer between 1992 and 1997. Functional status was assessed using Short-Form SF-36. Mean changes in health-related quality of life (HRQOL) scores was computed. Compared with women ≤40 years of age without breast cancer, women with breast cancer experienced a functional decline. Young women who developed breast cancer experienced the largest decline in HRQOL as compared with older women in multiple domains such as physical roles, bodily pain, social functioning and mental health. Much of the decline in HRQOL was age related (age ≥65 years).

A telephone survey was conducted from a random cross-sectional sample of 1812 Medicare beneficiaries aged ≥67 years treated for breast cancer 3–5 years earlier. The QOL and satisfaction with treatment were evaluated. The use of axillary dissection was the only surgical treatment that affected outcome, increasing the risk of arm problems fourfold (95% CI, 1.56–10.51). Having arm problems exerted a negative independent effect on all outcomes. Processes of care were also associated with QOL and satisfaction. Women who perceived high levels of ageism or felt that they had no choice of treatment reported more bodily pain, lower mental health scores and less general satisfaction. These same factors and also high perceived racism were significantly associated with diminished satisfaction with

the medical care system. The authors concluded that with the exception of axillary dissection, the processes of care and not the therapy itself are the most important determinants of long-term QOL in older women.[47]

Conclusion

Breast cancer in the elderly is inadequately diagnosed, with a significant delay. Many women are improperly treated, as there is a lack of practice guidelines for women above 65 years of age. Screening and prevention strategies need to be applied more rigorously to older women. The same therapeutic principles and selection criteria should be utilized as established for younger women. Breast care providers need to be cognizant of the associated illnesses and tailor therapy to suit the tolerance of the individual case.

Guidelines for therapy

The present knowledge base supports the following general guideline for the elderly:

- <4 cm tumour, ER+ → BCT + SLNB/ANC + RT + aromatase inhibitor.
- <4 cm tumour, ER− → BCT + SLNB/ANC + RT + chemotherapy; consider Herceptin.
- <4 cm tumour, ER+ → MRM + RT + aromatase inhibitor.
- <4 cm tumour, ER- → MRM + RT + chemotherapy; consider Herceptin.

Consider Herceptin in all HER+ cases who are eligible for chemotherapy. Consider downstaging for large tumours by neoadjuvant anastrozole/tamoxifen with or without chemotherapy prior to surgery. More elderly patients should be recruited in trials to expand the evidence base not confounded by ageist bias. Oncologists ought to explore newer modes of delivering less toxic chemotherapy, intraoperative radiotherapy and biological response modifiers. Interventions to address the physical and emotional needs of older women with breast cancer should be developed.

Key points

- Improve awareness among geriatric care providers for early diagnosis.
- Apply screening and prevention strategies similar to those applied to younger women to reduce the burden of disease and morbidity of therapy.
- Apply the same therapeutic principles as in younger women.
- Recruit more elderly women in therapeutic trials and develop practice guidelines.
- Be cognizant of comorbidity and tailor therapy accordingly.

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CHAPTER 111

Maintaining functional status

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Introduction

Cancers are largely diseases of ageing. The most recent SEER (Surveillance, Epidemiology and End Results) summaries through 2006 show that 61% of all cancers occur in people over age 65 years, an important fact for Medicare in the USA and similar health insurance programmes elsewhere. Age-specific rates continue to rise well into the ninth decade of life. Even though cancer mortality in the elderly is also higher and 71% of all cancer deaths occur in people of Medicare age, there are nonetheless 6.5 million cancer survivors over age 65 years, of whom 4.4 million are long-term, that is, >5 year, survivors. Therefore population studies of cancer and cancer survivorship are studies of ageing.[1,2]

Cancer is the leading cause of death for men and women aged 60–79 years, followed by heart disease. This is reversed among those aged 80 years and over, with heart disease causing more deaths than cancer.[3] Table 111.1 shows that cancer as a cause of death declines in importance relative to cardiovascular diseases in advanced old age.[3] As shown in Table 111.2, among the 10 most common cancers affecting adults, by a wide margin breast, prostate, lung and colon cancer occur mostly among the elderly.

In Table 111.3, it can be seen that the common cancers have good prospects for prolonged survival. All except lung cancer, if detected at an early stage, have better than a 50% 5 year survival.[3] Therefore, the goal of optimizing physical and mental function for elderly cancer patients and survivors affects hundreds of thousands of people. Treatment protocols tested in clinical trials have included few if any elderly participants over age 70 years, so individualizing cancer treatment for elderly patients requires individualizing functional assessments also.[4]

A role for geriatricians in cancer care

There is a strong referral bias for more fit elderly people in cancer clinical samples.[5] Clinical decision-making in cancer is further complicated by marked under-representation of elderly persons in cancer clinical trials.[6] Analyses of population treatment data through the linked SEER–Medicare database suggest that frail elderly people are unlikely to be referred to cancer specialists in community practice. Hurria *et al*.[7] performed standard geriatric functional screening on elderly CALGB trial enrollees and found that functional impairment defined as any ADL (activity of daily living), IADL (instrumental activity of daily living) or cognitive deficit was rare. For example, Gupta and Lamont[8] showed that the proportion of elderly with a diagnosis of dementia was lower among Medicare beneficiaries treated for colon cancer than in the general population. More recently, Lamont *et al*. used the SEER–Medicare database to compare treatment outcomes in community practice with those of trial participants and found that poorer results in the community treatment cohorts were not entirely explained by comorbidities.[9] Either trial participants were fitter regardless of comorbidity or receiving treatment through a trials centre conferred better clinical management.

Balducci adapted the consensus frailty phenotype as defined by Fried and co-workers'[10,11] to making decisions about cancer therapy.[12] He included ADL and IADL disability, non-cancer severe comorbidity and presence of 'geriatric syndromes' including cognitive impairment, falls and delirium as probably excluding an older cancer patient from receiving full dose or any chemotherapy.[12] Further, he effectively explained in terms of cancer-related life expectancy why frail elderly patients may be harmed with highly toxic therapy. There appears to be a tacit agreement in community practice not to subject obviously frail and otherwise incapacitated elderly people to toxic therapy.

The role of geriatrics in these decisions is to identify vulnerabilities that are not evident in apparently well elderly subjects, to prescribe and provide supportive interventions for patients with good prognosis cancers, to participate in the transition from disease control to symptom palliation and to communicate clearly with patients and families when the trajectory of disease is approaching end-of-life.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 111.1 Five leading causes of death: US men and women aged 60 years and older, 2009.

Age 60–79 years		Age 80 years and older	
Men	Women	Men	Women
Cancer	Cancer	Heart disease	Heart disease
Heart disease	Heart disease	Cancer	Cancer
COPD	COPD	Stroke	Stroke
Stroke	Stroke	COPD	Alzheimer's disease
Diabetes	Diabetes	Alzheimer's disease	COPD

Table 111.2 Five most common sites of cancer mortality: US adults, 2009.

Age 60–79 years		Age 80 years and older	
Men	Women	Men	Women
Lung	Lung	Lung	Lung
Colon	Breast	Prostate	Colon
Prostate	Colon	Colon	Breast
Pancreas	Pancreas	Urinary bladder	Pancreas
Oesophagus	Ovary	Pancreas	Non-Hodgkin's lymphoma

Table 111.3 Percentage 5+ year survival by cancer site, 1996–2004.

Cancer site	Survival rate (%)
All cancers	66
Prostate	99
Breast	89
Urinary bladder	81
Rectal	67
Colon	65
Non-Hodgkin's lymphoma	65
Ovarian	46
Oesophagus	17
Lung and bronchus	16
Multiple myeloma	16
Pancreas	5

Additionally, geriatricians inevitably care for long-term cancer survivors. Survivorship care entails awareness of cancer-specific sequelae. Survivors experience continuing adverse health for years after the event compared with those who never had a malignancy.[13,14] Ganz and Hahn[15] and others[16,17] therefore proposed specific survivorship care plans that go beyond mere surveillance for recurrences.

Functional status as used by geriatricians refers to activities of daily living (ADL), the ability to care for oneself at home, and instrumental ADL (IADL), the ability to live alone and manage one's own household affairs. This is different from oncologists' construct of performance status, which has more to do with exercise tolerance, grading activity levels from fully physically active outside the home to bedbound. Using a summary Karnofsky Performance Score (KPS)[17] or Eastern Cooperative Oncology Group Performance Score (ECOG-PS), oncologists make very accurate predictions about survival and ability to tolerate toxic therapies. Summary KPS or ECOG scores, however, are relatively insensitive to risk for functional decline and fail to identify the so-called vulnerable elderly. The summary scores do not identify specific functional disabilities that might be reversible, nor do they suggest how that might be done.[18] A short functionally based screening such as the ACOVE VES-13 has been proposed as a quick way to select apparently fit elderly cancer patients for further evaluation.[19,20] A more extensive battery of screening tools has been shown to be feasible to perform in the outpatient oncology setting.[7] Several studies have suggested that abbreviated geriatric measures of function provide actionable data.[21] For example, Extermann *et al*. addressed fall risk reduction for breast cancer patients.[22] Bylow *et al*. established a high prevalence of previously under-reported falls among prostate cancer patients on hormonal deprivation therapy.[23]

There have yet to be any randomized trials to test whether routine geriatric assessment could improve patient tolerance of cancer therapy. Cohen *et al*. reported a randomized clinical trial of continuity of care for geriatric veterans who received inpatient geriatric assessment and intervention with follow-up in outpatient GEM (geriatric evaluation and management) and home-based care.[24] *Post hoc* subgroup analysis revealed that older veterans with a cancer diagnosis benefited the most from geriatric continuum of care. Although they did not live longer, quality of life measures were statistically significantly improved.[25]

Staging the ageing of the elderly cancer patient

Cancer treatment often involves sequencing multimodal interventions including surgery, chemotherapy and radiation. There are several key aspects of geriatric assessment that are particularly salient for patients and physicians planning surgical cancer treatment. In addition to standard preoperative risk stratification, preoperative assessments should be able to anticipate whether subacute care[26,27] at home or at a long-term care facility (LTCF) will be needed. The goal is to prevent SNF placement but if it becomes necessary, selecting a LTCF or SNF (skilled nursing facility) on the day of discharge is disconcerting for families

and patients. Since it is usually predictable, shopping for acceptable facilities should begin early. If surgery will involve the head and neck or a long intubation, facilities' capacity to provide specialized oral care and speech and swallow therapies should be considered carefully, not just their ability to provide tracheostomy care. Nutritional support and evaluation are required to re-establish oral feeding.[28] Furthermore, early feeding when possible with use of protein–calorie supplements have been shown to improve surgical outcomes in elderly surgical patients.[29] Cancer surgery outcomes for the elderly are improved by early mobilization and early nutritional support.[26,27]

Use structured methods to establish decisional capacity prior to treatment

If chemotherapy is contemplated, geriatric assessments should be performed proactively to determine the patient's decisional capacity, that is, whether the patient is cognizant of the risks and benefits of the alternative courses. If there is any doubt, formal evaluation of decisional capacity is mandatory.[30] If decisional capacity is impaired, this should be factored into treatment decisions since at all stages of disease, cognitively impaired patients fare substantially worse.[8,31] Unrecognized cognitive impairment[32] and delirium[33] are common in elderly cancer patients. The complexity of the decision to be made needs to be titrated to the patient's cognitive capacity. There are four established legal standards for determining capacity: the patient is aware of the treatment options and expresses a treatment preference clearly and consistently; the patient can give a conventionally understandable reason that is consistent with their past behaviour; the patient retains and reproduces the information given as the context for the decision; the patient understands what their decision means for their own state of health.[30]

Figure 111.1 shows a schematic diagram of the decisional standard required to consent to each level of therapy offered. Physically robust, cognitively intact older patients have been shown to derive equal benefit from equal treatment in clinical trials and should not therefore be excluded from standard therapy and clinical trials on age alone.[6,34–36] Therefore, staging the ageing is as important as staging the cancer.

The diagonal axis in Figure 111.1 describes the ratio of risk to benefit for the course of treatment. The hierarchy of legal standards used to determine decisional capacity is arrayed on the *y*-axis. Usual care and clinical trials are marked on the diagonal suggesting the standard required for consent. Cancer care options are inclusive from least to most risky.

The short term impact of chemotherapy on functional capacity should be assessed proactively. Is the patient at risk for delirium? This bears directly on the patient's ability to self-manage chemotherapy-associated toxicities, medications and nutrition. What is the patient's home support system? An elderly person living alone who manages fairly well in their usual state of health is judged fit for chemotherapy by having an ECOG-PS of 2 or less. They are likely to do well in the infusion suite but may develop problems with delayed toxicities. It is critical that spousal, family or pre-emptive home care supports be put in place to prevent unplanned hospitalizations due to falls, delirium, malnutrition and volume depletion. The National Cancer Care Network (NCCN), which represents the largest number of community-based cancer treatment centres, has adopted these recommendations as part of its body of treatment guidelines for specific cancer sites in the elderly. An extensive summary statement of the evidence for these guidelines has been prepared by the International Society for Geriatric Oncology (SIOG) based in Geneva.[18]

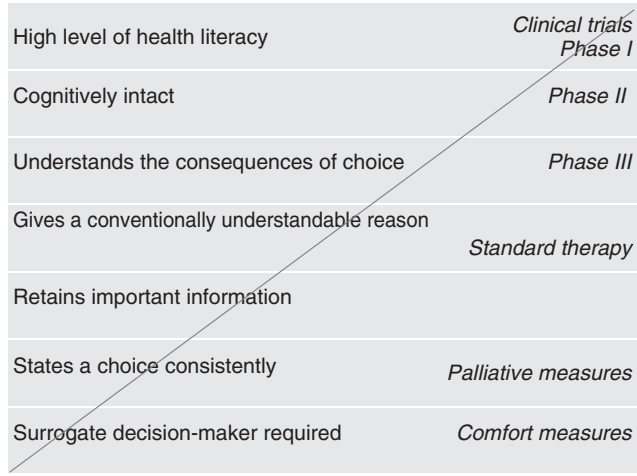

Figure 111.1 Matching the complexity of clinical decision-making to the decisional capacity of the patient.

Although numerous studies have reported that fit elderly patients tolerate cancer therapy without undue acute toxicities, elderly cancer patients have several specific chemotherapeutic risk factors. Dosing must be adjusted for reduced renal and hepatic function. Still, it has been well described that elderly patients experience more severe and more prolonged neutropenia from cytotoxic agents. Although studies are not entirely consistent, the NCCN has also recommends prophylactic use of granulocyte colony-stimulating factors to prevent neutropenia in elderly patients based on a high incidence of severe bone marrow toxicity observed in the elderly in clinical trials and increased risk for sepsis.[37,38] With the high risk for delirium, the use of 'prn' ('when necessary') advice to an elderly patient living alone, even with 'drop-ins', is simply not adequate. Outpatient management must prevent hospitalizations for toxicities which can spiral into loss of functional capacity and nursing home placement. Elderly

cancer patients should be vigilantly screened for risk of delirium and clinical suspicion should be high.[32]

Giving chemotherapy to a long-stay resident in an LTCF presents an array of complex medical decisions and ethical concerns. However, short-stay SNF residents may be receiving outpatient chemotherapy and radiation and the responsible nurses and physicians need to know what to expect. Hence transitions of care for elderly cancer patients are fraught with danger of communication lapses.[39] This is especially true since SNF care assumes, indeed based on the reimbursement codes, requires, functional improvement. Without a correct and clearly communicated cancer prognosis at the time of transfer, appropriate care cannot be given. Physician-to-physician communication by telephone, electronic record-sharing or writing is imperative. Prognostic errors go both ways, unrealistically optimistic and pessimistic, on both sides. The idea that an elderly patient with any malignancy is hospice appropriate can be as mistaken as the idea that a patient with an untreatable advanced malignancy can be functionally upgraded.

It often falls to the long-term care physician to state what was not clearly understood at hospital discharge. Over 65% of oncologists report that they do not routinely discuss prognosis, advance directives or end-of-life until the patient is within days to weeks of death. This contrasts with younger oncology physicians who report having these discussions before the need.[40] There is an interesting correspondence with patient preference in this study. A similar >60% of cancer patients preferred not to have these discussions with their oncologists; rather, they expressed no unwillingness to discuss advance directives and end-of-life with hospital doctors, which means typically hospitalists and house staff.[40]

Supportive management during cancer treatment is just good geriatric care

Supportive oncology is the branch of palliative medicine that addresses the management of symptoms due to cancer and to the debilitating effects of cancer treatment with the goal of maintaining patients' quality of life. All major cancer centres have invested in supportive care because it offers the best chance for patients to be able to complete treatment. When treatments fail and cancer progresses, supportive oncology manages the transition to hospice.

Four randomized clinical trials have compared palliative care delivered with cancer treatment to usual care with optional palliative referral as determined by the treating physician. Patients with advanced cancer in rural Vermont, $N = 322$, mean age about 65 years, were randomized to psychoeducational intervention with monthly telephone follow-up by advanced practice nurses. At the end of the study, quality of life and mood scores were higher in the intervention group, but there was no difference in symptom intensity or hospital days.[41] Two additional trials also showed improvements in self-reported quality of life among patients randomized to palliative care along with usual cancer care, but the differences were not statistically significant.[42,43] Similarly, a Norwegian trial was suggestive but inconclusive.[44] A more recent study reported that 151 advanced-stage lung cancer outpatients were randomized to concurrent palliative care or usual care. The mean age was again about 65 years. Mean change scores on symptom scales and quality of life scales favoured the experimental group, but the differences were not statistically significant. The experimental group survived on average 2.7 months (30%) longer and used fewer hospital days at the end-of-life.[45] One reason for the more definitive findings of this study is that participants were more homogeneous in terms of type and stage of disease and therefore had less variance in clinical course. Previous studies mixed different cancers and stages and lacked statistical power due to small numbers.

As with randomized controlled trials (RCTs) of geriatric interventions, it may not be possible to identify which interventions explain the results. That is, both GEM and palliative care involve multiple disciplines individualizing care, doing different things for each patient. This is a profoundly unsettling model of care for physicians trained to use drug trials of single agents, multidrug protocols in the case of oncology, to decide what works. It is unsettling to rely on questionnaire responses as endpoints over so-called 'hard' end-points such as disease progression, hospitalization and death. If similarly designed studies reproduce the finding of less hospitalization and longer survival, it shows that it is feasible to develop 'harder' evidence.

In the supporting oncology literature, it is clear that the burden of symptoms and also the stage of disease drive functional status. Targeting the most troublesome symptoms should improve functional status. The caveat in this literature is that the outcome measures, the portfolio of standardized symptom scales, are different from the functional geriatric measures, they are subjective, the numbers are small, patients are not particularly old and a variety of tumour types and stages are reported. The construct 'quality of life' includes functional status and a number of other things such as satisfaction, mood and energy. One review enumerated over 100 different definitions of quality of life.[46] It is easier to focus on studies of specific symptoms to sort out how treating that symptom affects quality of life, however it is defined. For example, a recently reported RCT of preventive treatment for chemotherapy-associated mucositis showed a significant drop in unplanned hospitalizations in the experimental group who reported less pain and better nutrition.[47]

In keeping with the purpose of this chapter, to focus on maintaining function and not on end-of-life, the next section addresses specific symptoms that occur during

cancer treatment, including pain, fatigue, nausea and vomiting and anorexia. Successful management of these symptoms can make the difference between loss of functional independence due to treatment and obtaining the benefit of treatment. The reader is referred to an excellent summary by Rao and Cohen.[48] Geriatricians immediately recognize the fatigue–anorexia symptom complex as age-related frailty. Supportive modalities include pharmacological agents, mind–body alternatives, rehabilitation and cognitive behavioural strategies. The following section looks at randomized trials of pharmacological agents. This is not intended to dismiss non-pharmacological, alternative and mind–body interventions. The level of evidence for these is weak but improving, reflecting the difficulty in designing and conducting trials of complex interventions. Readers are by no means dissuaded from trying them with willing patients.

Follow AGS guidelines to treat pain in the elderly cancer patient

There is not much more to be said about treating pain. People, patients, everyone functions better when the pain is treated. There is no plausible rationale for not treating pain, only that there may be different ways to treat pain and patients may differ in how aggressively they wish to be treated for pain. Cancer pain is complex. It is both nociceptive and neuropathic. There may be components of anxiety and depression. There are specific pain syndromes associated with surgeries, with radiation and tumour invasion plexopathies, bone pain and visceral pain, post-chemotherapeutic neuropathies and oral pain from mucositis. To the specialist, each has an appropriate treatment. Patients with specific surgical pain syndromes should be referred to specialist care, including head-and-neck centres, interventional pain clinics and postoperative rehabilitation centres.

The mainstay of cancer pain management has been the WHO approach to titrating non-opiate and opiate therapy.[49] The AGS pain management guidelines focus on how to assess pain in frail or cognitively impaired elderly and on caregiver education to recognize and treat pain.[50] Most moderate to severe cancer pain will respond to opiates. In the elderly, the conventional wisdom is to expect a higher peak effect due to a lower number of neural receptor sites (saturation) and a longer duration of action due to slower elimination. An advantage of opiates is the lower likelihood of gastrointestinal (GI) bleeding or renal failure compared with non-steroidal anti-inflammatory drugs (NSAIDS), but NSAIDS are particularly useful for bone pain. There is a higher risk for delirium, falls, nausea and constipation with opiates. In general, opiates with complex metabolism and active metabolites should be avoided, including meperidine, propoxyphene, fentanyl patches and methadone.[50] The geriatric practice of choosing the least number of agents by the least invasive route at the lowest dose is good advice with opiates. In general, short-acting agents are to be preferred, such as immediate-release morphine, oxycodone and hydromorphone, titrated under close scrutiny, especially for patients with impaired executive and short-term memory function. Opiates should always be accompanied by a bowel regimen to prevent constipation. Sennosides with stool softeners and osmotic agents together are preferred. Severe opiate bowel may precipitate hospitalizations. Methylnaltrexone is an injectable which blocks mu-opiate receptors in the bowel that does not cross the blood–brain barrier. It can be used for bowel rescue when oral agents fail.

Once the best level of pain relief versus sedation has been achieved, short-acting agents can be converted to a long-acting agent with breakthrough coverage using one of many available conversion tables or calculators. Adjuvants for neuropathic pain should be selected for lowest anticholinergic burden and evidence-based supporting literature. Consideration should be given to topicals, such as lidocaine gels and sports creams. Therapeutic massages, heat, cold, oral rinses and focused physical therapy all have a role. For example, moderate weight lifting proved superior to usual protective advice in reducing post-mastectomy lymphoedema pain in middle-aged women without affecting the actual volume of fluid retained.[51]

Treat fatigue in elderly cancer patients to limit functional decline

Considerable research has gone into understanding the non-pain symptoms of cancer and cancer therapy. Whether fatigue is the cause or the effect, elderly cancer patients who report extreme fatigue also report poor nutritional intake, poor sleep, immobility and loss of functional capacity.[52,53] Extreme fatigue is often a reason given for terminating cancer treatment. There are no specific diagnostic features to distinguish the fatigue of cancer from the fatigue of primary frailty. Both are characterized by unregulated cytokine production.[54] However, cancer fatigue generally dates to the clinical onset of cancer or to cancer treatment. Students of fatigue describe a multicomponent disturbance of neuroendocrine regulation, cytokine peripheral and central effects including depression and diurnal cycle dysregulation.[53] The association between cancer fatigue and anaemia is not as strong as initially thought, although severe anaemia certainly exacerbates fatigue. It has also been difficult to show a simple association between stage of disease and severity of fatigue or between specific treatment modalities and fatigue.[53] A follow-up study of clinical trial participants found that fatigue persisted years after the completion of presumably successful cancer treatment.[55] There is no consistent association between cancer fatigue and age.[52,53]

Fatigue outranks pain as a symptom for cancer patients.[52,55,56] It is a common complaint among frail elderly people who do not have cancer. Fatigue has been hard to define and hard to treat as it is embedded in a complex cluster of symptoms and disease-related perturbations. It has to be evaluated in the context of the disease trajectory and untangled from cancer-related anaemia, cancer treatment-related anaemia, radiation sickness and radiation-induced hypothyroidism, depression, disturbed sleep and undernutrition. Nonetheless, clinicians believe that it is a distinct cytokine-related syndrome. Studies have tried to define it and measure it so that it may be quantified. NCCN adopted a narrative definition: 'a persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion (related to cancer or cancer treatment) that is not proportional to recent activity and *that significantly interferes with usual functioning*'.[57,58] Provisional ICD-10 criteria for the E&M code include six of the following complaints: weakness, heaviness in the limbs, subjective problems with concentration and short-term memory, no motivation to participate in activities, a subjective sense of having to struggle to get moving, not getting the usual daily tasks done, feeling bad rather than pleasantly tired for several hours after exercise, sleeping too much or not enough and never feeling refreshed after sleep.[59] Minton *et al*. reviewed available standardized, validated fatigue screening and severity scales.[60–62]

Fatigue is worsened by depression. Depression is underdiagnosed among cancer patients.[61] Mor *et al*. have shown that elderly breast cancer patients are less likely to suffer from new onset depression than younger breast cancer patients.[62] However, in evaluating an elderly patient with fatigue, depression should be addressed routinely and explicitly.[18]

Symptomatic anaemia is treatable and should be treated in elderly patients, particularly those with underlying coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD) or increasing exertional dyspnoea. In one study, correction of anaemia with erythropoietin improved FACT-Fatigue scores but only if FACT-Anemia was also positive.[63] Recent clinical studies have dimmed hopes that erythropoietin supplementation for cancer-associated anaemias would solve the fatigue problem and have additional functional and survival benefits.[64] Transfusion or correction above 9–10 g dl^{-1} offered no further symptomatic improvement and increased the risk for thromboembolic and cardiac events.[65]

Research on the treatment of fatigue has focused on psychostimulants. The best studied is methylphenidate. A double-blinded placebo-controlled randomized trial of short-acting methylphenidate in cancer patients demonstrated improvement and maximum effect within 8 days and a sustained effect over the 4 weeks of the trial that was durable for up to 6 months on drug as measured by the Brief Fatigue Inventory (BFI). However, there was no statistically significant difference between the treated arm and the placebo arm except among patients with BFI-rated >6, severe fatigue.[66] Sustained-release methylphenidate showed benefit equivalent to short-acting methylphenidate in a trial enrolling patients undergoing cancer treatment and was also not different from placebo except among the subgroup of patients with BFI >6, severe fatigue.[67] A head-to-head comparison of methylphenidate and modafinil favoured methylphenidate.[68] Two trials have been reported that tested whether donepezil effectively addresses the cognitive component of cancer-related fatigue. Patients treated with donepezil reported 56% improvement of fatigue symptoms, not different from placebo.[69] A randomized trial of placebo versus 'no-cebo' reported 56% improvement of fatigue symptoms on placebo versus 36% on 'no-cebo'.[70] In summary, if there are no contraindications, methylphenidate appears to be safe for a trial of treatment for severe cancer-related or cancer treatment-related fatigue in elderly patients.

Anticipate anorexia, recognize cachexia and support nutrition

Anorexia means loss of appetite. Loss of appetite and distortions of taste commonly occur in cancer patients and it is critical to determine whether the symptoms are due to the cancer or to cancer treatment. If anorexia causes failure to eat and weight loss, and the patient is not at end-of-life due to the cancer, it is reasonable to try to stimulate appetite and nutritional intake.[29,71] The key differential diagnosis is to recognize cancer cachexia, a cytokine-mediated hypercatabolic state in which both fat and muscle are degraded. Cytokines have central effects on appetite and peripheral effects on metabolism.[72–74] Cancer cachexia, unlike protein–calorie starvation, is not reversible solely with nutritional interventions.[75] Some cancers induce cachexia early in their course and treating the cancer may induce a brief period of remission with improved appetite and possible modest weight gain. Pancreatic cancer is highly inflammatory and is one such example. Among the common solid tumours including non-small-cell lung, prostate, breast and colon, rapid weight loss occurs late in advanced disease and signals impending death. Haematological malignancies in general do not precipitate cachexia, although immunotherapies may.

In starvation, resting energy expenditure declines and metabolism slows to divert available calories to high-priority end-users such as the brain and heart. Patients with very poor intake can sometimes maintain a remarkable level of physical activity. Hence it is crucial to differentiate weight loss due to cachexia from just poor nutritional intake with or without anorexia. In cancer patients, there may be physical causes for not eating even if hungry. Mucositis, radiation

oesophagitis, diarrhoea and nausea, surgical interruption of the GI tract, pain, sedation and drug effects affect eating. Families are often more anxious about disturbances of appetite than the patient in the author's experience. Treating proximal symptoms can improve intake. High caloric density snacks and liquid protein–calorie supplements are easy to consume and not over-filling.

Anorexia has been the subject of a number of randomized clinical trials. There are four basic classes of orexigenics. Corticosteroids, dexamethasone 4 mg 1–4 times per day or prednisone 5–10 mg per day initially induces a mild euphoria, suppresses nausea and may increase appetite. The risks include further immune suppression, Cushingoid changes with long use, myopathies, HPA (hypothalamic–pituitary–adrenal) axis suppression and hyperglycaemia.[76] There is no convincing evidence that they cause weight gain with short-term use and the weight gained with prolonged use is largely fat and water. The progestationals are the best studied orexigenics. These include megestrol acetate 400–800 mg per day or medroxyprogesterone 500 mg twice daily.[76] As shown by Yeh *et al*. in an RCT that did not include cancer patients, frail veterans did gain weight and the maximum effect was seen by 12 weeks of treatment. After 1 year there was no difference in the weight of the experimental and control groups.[77] On treatment, participants had lowered cytokine levels.[78] There is an increased risk of venous thromboembolism with progestationals and potential for HPA suppression, so they should be tapered once the treatment goal has been reached or stopped if no response is obtained after 12 weeks.

Cannabinoids include medical marijuana, which is not usually considered for elderly patients regardless of diagnosis, and dronabinol 2.5–20 mg twice daily. One widely cited study of advanced HIV patients showed improved appetite but no weight gain after 1 year.[79] A head-to-head comparison of megestrol acetate (MA) and dronabinol in 469 cancer patients was reported. The 73% of patients randomized to MA reported better appetite and 13% gained >10% of their starting weight compared with 47% and 3%, respectively, in the dronabinol group. There was no added benefit to combining the drugs and the older patients did not tolerate the dronabinol.[80] Recent reports suggest a role for the novel GI peptide ghrelin in managing cancer-related anorexia.[81,82] A number of novel agents, including SARMs (selective androgen receptor modulators) and anti-TNF (tumour necrosis factor) antibodies, have been studied in small numbers of subjects and second-look studies of atypical antipsychotics, thalidomide and anabolic steroids including oxandrolone are under way, but so far definitive evidence is lacking.[83]

Anticipate and prevent nausea and vomiting

Nausea and vomiting are a normal part of the host defence system among omnivores and carnivores that is not shared by ungulates. It is designed to rid the body of toxic ingested substances. The physiology of nausea is shown in Figure 111.2. The area postrema at the base of the fourth ventricle where the blood–brain barrier is permeable provides early central sensing of toxins in the bloodstream. Stimuli are forwarded to the vomiting centre in the medulla to coordinate the vomiting reflex with feedback to the upper GI tract. Central causes of nausea and vomiting include increased intracranial pressure, vestibular toxicity, motion sickness, acid–base disorders, electrolyte disturbances, chemotherapy and anxiety, so-called anticipatory nausea and vomiting. Elderly patients have been described as less likely to suffer from anticipatory nausea and vomiting than younger patients.[84] Many anticancer drugs cause nausea and vomiting.[85] Opiates are also highly likely to cause nausea and vomiting, particularly in the opiate-naïve patient and when doses are rapidly escalated.

Chemotherapeutic agents are ranked as minimally to highly emetogenic and infusion therapists generally incorporate premedication into the protocol to prevent acute chemotherapy-induced nausea and vomiting (CINV).[85] Perhaps because of less anxiety or because of the selection of less toxic chemotherapeutic agents, elderly cancer patients appear to suffer less with acute CINV. Delayed CINV is also well described and it is a more serious problem for elderly cancer patients. Around 4–10 days after chemotherapy, it is caused by a combination of central and peripheral disturbances and by direct GI tract toxicity. Specific toxicities include oral and pharyngeal pain, digestive endothelial mucosal injury due to cytotoxins and antimetabolites, radiation, increased vagal tone, autonomic failure, hiccups associated with phrenic nerve and diaphragmatic irritation. Gastritis, gastric reflux and gastroparesis cause nausea. These problems are often accompanied by severe diarrhoea and a high risk for volume depletion, falls, delirium and injury.

Elderly patients undergoing chemotherapy should not be left alone or treated with prn measures during this vulnerable period. When the acute infusions go well it may be assumed that there is no further problem. An able caregiver should be present at all times and preventive treatment of side effects should involve scheduled dosing, not as needed. Non-pharmacological treatment has limited efficacy. Small, frequent snacks of preferred foods and liquids may be all that is tolerated. The choice of drugs should be identified as closely as possible to the presumed aetiology with the understanding that there is a large placebo effect.[76,86]

Six classes of agents are available for control of central and upper GI-induced nausea and vomiting. Benzodiazepines are useful for anticipatory CINV and to induce sleep. Opiate-related nausea should be treated if possible with dose reduction or rotation of drugs. Central nausea is helped by a variety of agents as shown in Figure 111.2. There are currently three serotonin 5-HT3 antagonists

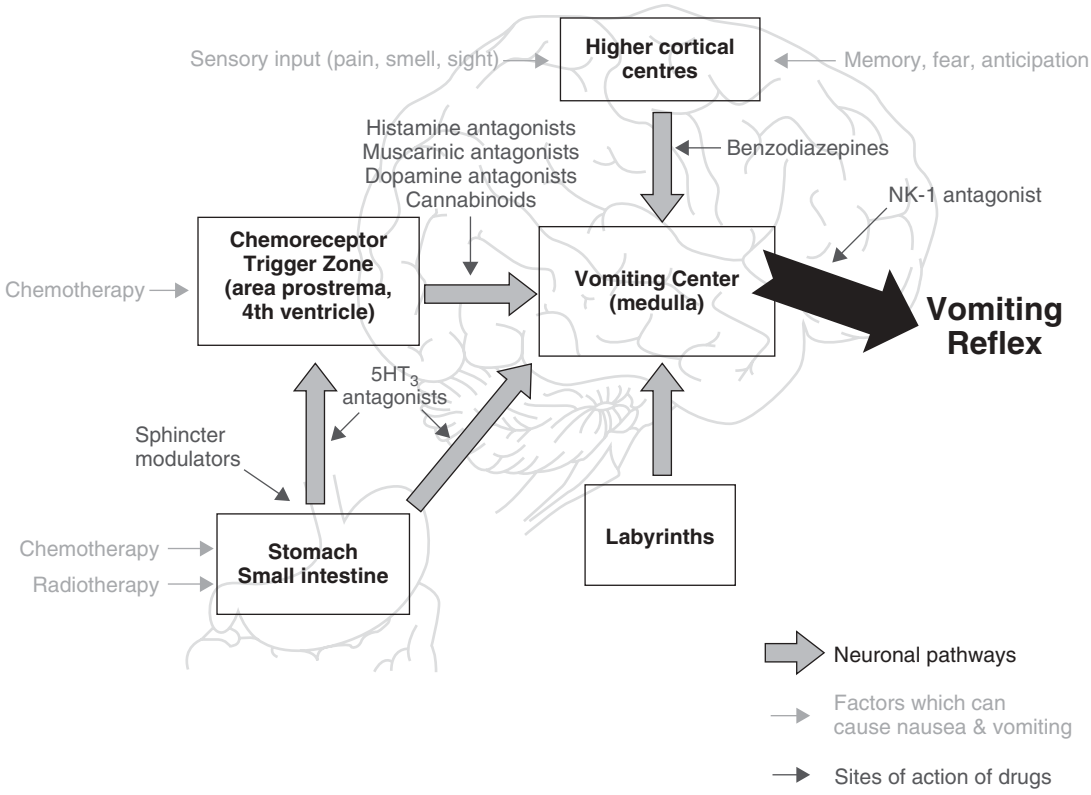

Figure 111.2 Nausea and vomiting pathways.

available, ondansetron, granisetron and dolasetron. They are favoured for effectiveness and lack of side effects. Generics are becoming available. A newer agent, the NK-1 receptor agonist aprepitant, blocks substance P in the medulla to the vomiting centre. Antihistamines include H1 blockers such as diphenhydramine and meclizine. Several D2 blockers, including prochlorperazine, chlorpromazine, metaclopramide and haloperidol, are used for their antihistaminic effects and also sedation. Anti-M1 muscarinic agents include atropine and scopolamine and act on the pathways between the chemoreceptor zones and the medulla. Anticholinergic side effects should be expected. The mechanisms by which corticosteroids manage CINV are not known. Dexamethasone 4 mg four times per day and 8 mg twice daily or prednisone 10 mg daily for 3–4 days have been used prophylactically to cover acute CINV. This treatment is usually combined with metaclopramide and a 5-HT3 antagonist.[76,86]

Delayed CINV is treated with 5-HT3 antagonists. Cannabinoids have fallen out of favour for this indication among medical oncologists. There is considerable popular support, however, for legalizing medical cannabis. Gastroparesis can be treated with promotility agents such as metaclopramide.[86] Physicians need to review carefully all the medications that the patient is taking in order to minimize polypharmacy, especially non-cancer drugs that may aggravate GI symptoms such incretin analogues for diabetes, calcium channel blockers, iron supplements, other anticholinergics and antihyperglycaemics that can cause severe hypoglycaemia when the patient stops eating.

Exercise

Exercise maintains function. How good is it for elderly cancer patients and survivors?

The impact of exercise on functional status and disease management has been reported to be beneficial for the management of frail elderly patients[87] and many of the common chronic illnesses. Cancer is a somewhat different proposition. First, it is not one disease. The functional impact of cancer depends on both the type and the stage. Furthermore, cancer treatments vary considerably in how debilitating they are to the patient. Whether to treat the cancer or only the symptoms may depend as much on a patient's performance status as it does on the effectiveness of the cancer treatment. The value of exercise in cancer treatment is of great interest and some complexity. In summarizing this literature, it will be noted that virtually no studies have explicitly addressed exercise for elderly cancer patients despite the fact that they are the majority of

patients and the majority of survivors. It is therefore, like chemotherapy trials, a problem in extrapolation. We can see what kind of cancer patients were exercised and we can estimate the extent to which elderly people with cancer fit this profile.

How cancer affects exercise tolerance

A sedentary lifestyle is associated with low cardiorespiratory fitness. If inactivity due to pain, cytokine-induced fatigue, nausea, anorexia, treatment-induced fatigue, joint pain,[88–90] mucositis, neuropathy and diarrhoea is superimposed on pre-existing disuse atrophy and inactivity, tolerance is further affected.[57] One survey of cancer survivors confirmed that 70% are sedentary.[91] Observational studies also confirmed that activity levels drop during cancer treatment, generally after the second or third cycle of chemotherapy, and are unlikely to return to pretreatment baselines.[92,93] A second survey of cancer patients during and after treatment reported that 70% of respondents engaged in exercise over this period, but this survey has limited generalizability since 66% of the respondents were white, married women under 60 years of age and 88% were rated as 90% or better KPS by their physicians.[94]

The combined effects of pre-existing organ dysfunction, tumour cachexia and drug toxicity need to be disaggregated in order to understand the role of exercise in cancer. For example, the oxygen consumption of middle-aged postpneumonectomy patients was shown to compensate out of proportion to the volume of lung resected.[95] It is unclear whether this would be replicated in aged patients with age-related loss of lung compliance. Two small pilot studies by the same group reported fewer perioperative complications among patients with a mean age over 65 years and resectable lung cancer who were given preoperative conditioning exercise.[96,97] Although the idea of neoadjuvant physical training prior to cancer surgery, as in elective joint replacement surgery, is intriguing, no studies of other tumour types have been reported.

In a follow-up study to a preoperative lung resection study, the investigators found no change in pre- and post-exercise inflammatory markers.[98] Similarly, 10 young patients with acute leukaemia were exercised during induction therapy with self-reported improved mood and endurance, but no change in cytokine levels was observed.[99] Little can be generalized from these small studies. Results may be affected by limited variability in measures of cytokine activity, small numbers and the brief intervention. The fact that observations were concurrent with pro-inflammatory treatment may also mask an effect.[75] In patients who already have advanced chronic disease such CHF and COPD or primary frailty, background inflammation may well have preceded cancer effects. As had been shown, cytokine levels are also associated with non-cancer frailty.[54,100]

Choosing appropriate exercise along the trajectory of disease

The onset of rapid wasting, exhaustion, anorexia and weakness is a sign of advanced cancer and portends imminent death.[101] In this setting, physical therapy and exercise need to be evaluated for whether they provide pain relief or other comfort. It is not credible, at least to the author, that functional improvement or strengthening is an appropriate goal for dying patients. A cancer diagnosis, especially a verified diagnosis of metastatic cancer, is a hospice-qualifying diagnosis, but as the diagnosis and actual survival are poorly correlated, the rapid decline in performance status is a better prognostic indicator for cancer survival. A dying patient cannot benefit from rehabilitation. However, a patient with a cancer may not imminently be dying. Typically, hospice companies will not pay for restorative therapy to return a patient to a previous level of function on the presumption that a terminal diagnosis means irreversible decline. Conversely, eligible patients who are not offered hospice care or refuse hospice admission may have no way to afford long-term care and so their Medicare Part A benefits are used for 'subacute' even when death is near. A skilled clinician ought to be able to make a reasonably accurate diagnosis of early death. As shown in Figure 111.3, functional decline due to advanced cancer is usually irreversible. This contrasts with the up-and-down course of other end-stage diseases such as CHF and COPD in which some functional recovery after exacerbations is the rule.[101] It is reasonable to provide gentle mobilization therapies, therapeutic massage and mind–body interventions to patients with advanced malignancy who want them and who are able to participate. However, it is also appropriate to withhold restorative therapies for patients with advanced malignancy who are dying, the last stage of a predictable course of disease.

Figure 111.3 tracks the functional status over 1 year of two geriatric outpatients that the author cared for. One was a 76-year-old woman with mild dementia and colon

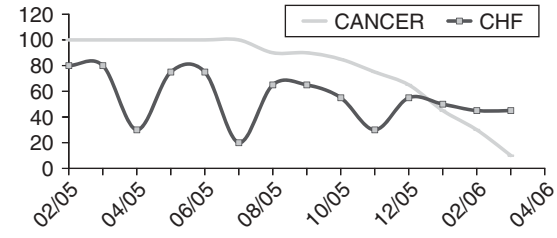

Figure 111.3 Comparing the course of chronic disease to cancer. The *y*-axis is the Karnofsky Performance Score and the *x*-axis is the time course over 12 months.

cancer receiving single-agent maintenance for what had been stable Stage IV disease. The other patient was an 85-year-old man with CHF, NYHA Stage II–III, and recurrent hospitalizations. It illustrates the observations of Teno *et al*.[101] that with many chronic diseases, the course of the final year of life is often difficult to predict but cancer is quite predictable.

There are few data on the benefit of rehabilitation in patients with advanced malignancy. Jones *et al*. reported accrual data for their study of exercise for inoperable lung cancer patients. Of the 20% who were fit enough for exercise screening, 40% consented. Hence only 8% of non-operative stage lung cancer patients were willing and able to exercise.[102] In another study, less than half of 25 highly selected patients with advanced lung cancer enrolled in a feasibility study were able to complete an 8 week fitness programme.[103] At the very end of life, complementary therapies might be more helpful. Stretching, yoga, massage and relaxation therapies are likely appropriate physical modalities for end-of-life cancer patients.[104] Long-term care facilities are often enough given the job of recognizing an imminently terminal prognosis when patients are sent from hospitals with inadequate records and no clear understanding of life expectancy.[39] In this situation, adequate consultation for prognostication is an important part of care planning.

Exercise and radiation toxicity

Radiotherapy is a rapidly evolving field. Radiation oncologists undertake a variety of dose modulation, shielding and pharmacological measures to limit healthy tissue damage. However, they also recognize that there are long-term delayed pulmonary and cardiac toxicities experienced by lung, lymphoma and breast cancer patients treated for loco-regional disease.[105] No study has actually evaluated the effect of pulmonary rehabilitation on post-radiotherapy pulmonary function. Some degree of permanent scarring is inevitable.[106] Patients with poor cardiopulmonary function measured by the 6 min walk distance (6MWD) sustained greater tissue damage after palliative radiation for inoperable lung cancer than did fitter subjects.[107,108] One small trial reported generally positive but essentially marginal performance benefit to patients with mixed tumour types who exercised at home during outpatient radiation therapy.[109]

Exercise and chemotherapy toxicity

Several chemotherapeutic agents have toxic effects on cardiopulmonary fitness. Specifically, the anthracyclines, which are among the most effective agents for lung and breast cancer, ovarian cancer and lymphomas, have direct cardiac myocyte toxicity.[110–112] Oncologists now will generally avoid using anthracyclines in elderly and heart patients if there is an acceptable alternative. However, the current cohort of long-term survivors did receive these agents when they were younger and the debt is coming due. Primary care physicians may not have access to chemotherapy records from the past.

New biological agents such as bevacizumab, an anti-VEGF monoclonal antibody, show effectiveness in treating a number of cancers by blocking their ability to grow an arterial supply. However, early on in trials with breast cancer patients, excess cardiovascular mortality was seen in older women and it is not recommended for older patients.[12] Trustazumab was very effective in Her2+ breast cancers, but the benefit was deemed marginal in elderly women, even those with appropriate histology.[113] The '–abs' are one class of targeted agents, the tyrosine kinase inhibitors (TKIs), that are not directly cytotoxic to cancer cells but rather modulate their ability to sustain oxidative metabolism and to migrate. Nearly all in common use have been shown to have cardiotoxic potential.[114] They are relatively new agents that early on showed excess toxicity in elderly patients, but long-term effects for survivors are not yet known.

The effect of exercise on TKI toxicity has been examined in only one study. Middle-aged women with Her2+ breast cancer were provided with supervised aerobic exercise during 4 months of adjuvant trustazumab therapy; 17 women experienced statistically significant LV dilation and reduced ejection fraction despite training.[115] These findings do not support the speculation that exercise during chemotherapy with TKIs is cardioprotective, but there was no control group so it is possible that cardiotoxicity was lessened by the intervention. Further empirical studies are needed.[116] Since aerobic and resistance exercise promote angiogenesis in muscle, there is a theoretical reason to think that exercise could also promote tumour angiogenesis.[95]

IGF-1 is another growth factor implicated in tumour growth. Several solid tumour cell lines express IGF receptors that present targets for new blocking agents. Observational studies have noted an association between fasting insulin levels in non-diabetic women and time to progression in breast cancer patients[117] and in colon cancer patients.[118] Exercise increases insulin receptor sensitivity and decreases insulin secretion. Strength and endurance training lowered insulin levels in breast cancer survivors in two randomized trials but the effect on late recurrence is unknown.[119,120] Limitations of these studies were small numbers, brief follow-up and relatively younger participants. Furthermore, the interventions were intense, requiring supervision in exercise physiology laboratories. Whether similar results can be obtained in community settings with elderly patients is the subject of current research.

Breast and prostate cancer survivors experience accelerated ageing

Support for the general efficacy of exercise interventions would require showing that elderly representatives of community-living elderly would adhere to an intervention that is rigorous enough to achieve endpoints such as modifying cardiovascular risk factors, markers of inflammation and measures of fitness and body composition. Such trials have been reported. Project LEAD randomized 182 recently diagnosed older breast and prostate cancer survivors to a home-based diet and exercise intervention.[121] A follow-up study randomized 641 >5 year survivors of breast, prostate and colon cancer aged 65–91 years to a home-based programme. Their self-reported SF-36 physical function sub-scale scores declined less in the intervention group. The intervention group increased their exercise time on average by about 15 min per week and on average the intervention group lost about 1.1 kg more weight.[122] Nearly all of the self-reported comparisons were favourable and statistically significant for the intervention group, but no physiological measures were taken and actual clinical improvement is to be inferred. A trial of supervised exercise in 177 middle-aged women showed marginal increases in 6MWD after a 12 week intervention that was maintained for 6 months.[123]

Main-line therapy for oestrogen/progesterone receptor-positive breast cancer is now daily oral aromatase inhibitors to deprive residual tumour of trophic oestrogen. The anti-cancer effectiveness of these agents appears to result in exaggerated adverse changes associated with endocrine ageing, including worsening of cardiovascular risk factors and accelerated bone loss.[124] Standard of care for postmenopausal women on aromatase inhibitors includes measuring their bone mineral density (BMD), supplemental vitamin D and bisphosphonate therapy.[15] The aromatase inhibitors and bisphosphonates have both been associated with bone and joint pain.[88,125] Because these women experience adverse changes in cardiovascular and bone health risk factors, they are an important target for exercise interventions aimed not at the cancer but at the adverse risk factor profiles induced by cancer therapy. One systematic review focused on trials of endurance and resistance training immediately after initial treatment of breast cancer (54% of all subjects in all trials), prostate cancer or all other cancers. They concluded that there was support for improved oxygen consumption and one-repetition arm or leg strength, but no effect on body composition or other physiological measures.[126] Most studies were of small size and short duration and suffered other methodological weaknesses such that fitness measures ought to be regarded as intermediate measures for a potential risk reduction that has yet to be shown. The studies were also not explicit as to whether the risk reduction of interest was for cancer recurrence or for cardiac outcomes.

Early studies documented the basis for women's complains of weight gain during breast cancer treatment.[127] Small studies showed that this adverse effect was blunted by vigorous exercise.[128] The small studies were positive and likely reflect a publication bias. Larger studies later confirmed the benefit of multimodal fitness training for overall wellbeing, strength, curbing weight gain and improved activity levels, except among women who received anthracycline treatment.[129] Two systematic reviews that included many of the same studies confirmed a generally beneficial effect for measures of performance, but were unable to draw conclusions about metabolic outcomes due to inconsistent reporting of biochemical markers of cardiovascular risk.[130,131] Most recently, Friedenreich and colleagues reported on a large RCT of 320 sedentary post-menopausal breast cancer survivors who engaged in supervised aerobic activity for 45 min per day for 5 days per week for 1 year. After adjusting for weight loss from baseline, the treatment group had statistically significantly lower estrogen levels than the observational control. Androgen levels in these women did not change.[132] The investigators did not report on changes in lipids, inflammatory markers, fitness outcomes or the radiodensity of mammograms, but they did demonstrate that sedentary women can be engaged in vigorous exercise.

Observational studies appear to support the interventional studies. The Nurses Study followed nearly 3000 women after the diagnosis of breast cancer and found about a 6% lower mortality from hormone-sensitive breast cancer between the lowest quintile <3 MET (metabolic units) per week and the upper half >9 MET per week activity levels. The highest quintile experienced no additional benefit.[133] A similar reduction in cancer-specific and total mortality was observed among 668 male physicians followed after treatment for localized colon cancer. The median exercise level was 18 MET per week. Men who exercised >27 MET per week had a relative risk reduction (RRR) of about 50% compared with sedentary men on <3 MET per week.[134] The usual caveats apply to these observational data since there may be numbers of unmeasured covariates. For example, the burden of progressive disease may have been much lower among the active survivors, explaining their higher activity levels. This bias is attenuated but not entirely removed by statistical adjustment for stage of disease.

Androgen ablation is the cornerstone of prostate cancer management. Achieving castrate levels of endogenous testosterone deprives prostate cancers and satellite metastases of hormonally mediated growth factors. Prostate cancers remain hormonally susceptible for a median of 6 years before they develop hormone independence. Because of this, many urogenital oncologists are less eager to

treat biochemical recurrences in the absence of evaluable disease.[135] Five year survival after a diagnosis of prostate cancer, for example, is well over 90%.[3] However, increasing evidence for long-term adverse effects of androgen deprivation on cardiac risk and physical performance are accumulating.[32,90,135–140] Androgen ablation affects men in many serious ways. Hot flashes, fatigue, loss of libido and depression are subjective toxicities. Loss of muscle mass and increased body fat are recognized side effects.[139] The adverse change in body composition also contributes to the observation of increased incidence of type 2 diabetes and cardiovascular disease.[136,141,142] Our consecutive series of elderly men attending prostate cancer clinic reported an unexpectedly high rate of falls.[23] Combined with hypogonadal bone loss, the risk for fractures is increased.[137,140,143]. Epidemiological associations with physical activity[144] provide part of the rationale for trials of extreme lifestyle interventions for men with prostate cancer.[145,146] Severely restricted diets, especially those with low protein content, are potentially dangerous for elderly men experiencing accelerated muscle ageing due to hormonal manipulation.

Given the well-understood toxicities of androgen ablation in elderly men, it is surprising that so few exercise intervention trials have been reported.[147] The standard of care has acknowledged these. Loss of muscle is measurable before 1 year of therapy is completed.[138] Hence current guidelines include using pulsed androgen ablation to limit toxicity, measuring BMD and giving prophylactic bisphosphonates.[135] Into this gap one group has reported a well-designed trial aimed at metabolic risk factor modification. The RADAR trial plans to enrol 370 men undergoing androgen ablative therapy from multiple sites in Australia. They were randomized to 6 months of supervised resistance and aerobic exercise versus standard public health recommendations for exercise for cardiovascular health.[148] Their report of preliminary findings with the first 60 subjects at 12 weeks is encouraging. There were statistically significant increases in muscle mass, strength and gait speed over short distances and significantly improved rapid clinical balance test (backward gait speed). The authors caution about ceiling effects due to selection bias. C-reactive protein levels dropped significantly in the intervention group, but there was no change in body composition, lipid total or fraction levels, insulin, homocysteine or blood glucose. The authors attribute this disappointing aspect of the trial to the short duration of exercise participation and to the less than 250 min per week of aerobic exercise in the protocol.[149]

Exercise and subjective quality of life

Physical exercise is the most widely studied intervention to treat cancer fatigue. Several systematic reviews have evaluated exercise interventions to relieve cancer fatigue.[93,150,151] Part of the difficulty in performing these analyses is the overall poor quality of studies. Some were restricted to one tumour type, others were mixed. Some involved variations on circuit training with resistance and aerobic conditioning components. Others examined mild activities such as walking or walking and stretching. Relatively few were randomized and controlled and all but a handful were crippled by small numbers. The most common endpoint was subjectively rated fatigue. Several studies measured fitness outcomes including gait speed, muscle strength and aerobic performance. The association between physical training effects and subjective fatigue was not as direct or as simple as expected. In other words, fit and fatigued was as common as fit or fatigued.

Of the main group of studies, subjects over the age of 65 years were routinely excluded. In a systematic review, 19 of 34 studies enrolled participants over the age of 65 years.[152] Four of 19 studies enrolled only subjects over 65 years old.[153]. One meta-analysis concluded that the benefit was probably real but small. Calculated effect sizes were less than 0.5 SDs in nearly all comparisons.[130] The most recent meta-analysis found 28 of 54 published studies to be adequate for analysis.[150] While adjusting for heterogeneity, the analysis did not attempt sensitivity analysis to control for publication bias. The analysis found consistent positive findings for exercise compared with no exercise controls. The largest effect sizes (ES) were reported for the breast cancer subgroup of 18 studies ($N = 977$), ES–0.36 (95% CI,–0.49 to–0.23). and for 11 studies ($N = 491$) comparing exercise with no exercise among long-term survivors, ES–0.37 (95% CI,–0.55 to–0.18).[154] Another group of investigators reported that elderly women aged over 75 years adhered poorly to their exercise protocols and were therefore pessimistic about this intervention.[155] It is possible that their protocol was not 'gero-friendly' and that age-tailored interventions would obtain better adherence.

Although the best clinical trial evidence in cancer patients is graded as only moderate in quality and weakly supportive of structured exercise interventions, for the elderly in general the evidence of benefit of increased physical activity is broadly supported. Table 111.4 presents an heuristic algorithm with no empirical evidence that attempts to summarize the results of published research as a prescriptive model for exercise in elderly cancer patients and cancer survivors. It should be validated empirically. As a 'thought experiment', scores <4 suggest that exercise is unlikely to be beneficial or accepted. Scores of 4–5 suggest that symptomatic relief of fatigue and stiffness through low- to moderate-intensity exercise would be beneficial. Scores of 6 or more suggest moderate-intensity training, such as structured walking programmes and resistance training, would be beneficial for long-term survivors. Baseline performance can be estimated from any validated, available activity questionnaire or standardized observational fitness

Table 111.4 A proposed algorithm for exercise prescription for elderly cancer patients.

Item	Points
1. Current exercise capacity[a]	
Immobile (PS 3–4)	0
Sedentary but mobile (PS 2)	0
Low-intensity exercise (PS 1)	1
Moderate-intensity exercise (PS 0)	2
2. Estimated remaining life expectancy with cancer	
<6 months	0
1–2 years	1
3–5 years	1
>5 years or cure	2
3. Duration and toxicity of current cancer therapy[74,85]	
Intense high-toxic therapy, e.g. bone marrow transplantation	0
Episodic high-toxicity therapy with no therapy while in remission	1
Continuous low-toxicity cytotoxic therapy depending on continued response	1
Continuous hormonal or pulse deprivation[b]	2
Long-term survivor on no anticancer therapy[b]	2
4. Patient exercise goal	
Comfort	0
Symptom management	1
Health improvement	2

[a]Reverse scoring of ECOG-PS: 0–1 = 2, 2 = 1, 3–4 = 0.
[b]May require cardiac risk stratification.

evaluation. Estimating remaining life expectancy eliminates the need for an age-based scoring requirement.

For example, an 80-year-old man on androgen deprivation therapy maintains a moderately active lifestyle. He walks every evening with his wife. He accrues one point for life style, two points for therapy and one point for estimated life expectancy. His choice of symptom management only for hot flashes and fatigue vs choosing health improvement for maintenance of strength and muscle mass adds one point to total five with a recommendation to continue moderate exercise.

In another example, a 75-year-old woman is diagnosed with estrogen receptor-positive breast cancer. She chooses not to undergo lymph node sampling, fearing postoperative lymphoedema. She is treated with simple mastectomy and an aromatase inhibitor. She has multiple comorbidities, including arthritis, NYHA Stage II congestive heart failure, diabetes and Stage II chronic renal insufficiency. She is able to do light housekeeping and drive a car, but she engages in no regular exercise. She accrues no points for lifestyle, one point for survival based on her comorbidities, two points for rigour of cancer therapy and she prefers symptom management. Her points total is four and a prescription for light weight-bearing exercise such as walking to maintain mobility and for bone preservation would be appropriate.

Conclusion

Elderly patients with a new diagnosis of cancer are heterogeneous and the specific cancer diagnosis introduces another layer of complexity to clinical decision-making. Decisions about treatment must take into account the patient's functional status and remaining life expectancy. Clinicians must be able to distinguish with some certainty whether impairments in functional status are attributable to age-related frailty, non-cancer comorbidities or the malignancy. Geriatric assessment screening tools have been proposed as a way of stratifying geriatric risk for cancer treatment toxicity. Several expert bodies now recommend routinely assessing for ADL and IADL dependency, and screening for falls, delirium and depression, for cognitive impairment and nutritional deficits. In some cases, directly observed performance measures are helpful in determining danger of falls and functional decline during treatment. Determining whether there is adequate caregiver and social support is also crucial as a safety net if disease or treatment effects cause falls, delirium, malnutrition and unplanned hospitalizations leading to functional decline. Highly selected fit elderly patients in clinical trials appear to derive equal benefit from equal treatment. Specifically, cognitively impaired patients fare poorly in cancer treatment, with excess mortality and questionable benefit.[31] Both physical frailty and decisional incapacity will preclude aggressive cancer treatment.

Limited clinical trial evidence suggests that elderly cancer patients benefit from geriatric interventions during and after treatment. Clinical trial evidence suggests that formal and continuous palliative interventions in addition to usual cancer care may improve quality of life measures and possibly survival. For the elderly cancer patient, proactive management of treatment toxicity is critical to maintaining function and preventing hospitalizations for treatment-related toxicity that lead to further functional decline and loss of independence. Important acute toxicities include mucositis and poor oral intake due to radiation and cytotoxic chemotherapy, volume depletion from poor intake, vomiting and diarrhoea. Elderly patients appear to suffer less acute and more delayed nausea and vomiting, hence treatment should be preventive rather than reactive. Anorexia with weight loss must be distinguished from cancer cachexia. Proactive pharmacological symptom management and nutritional support are necessary during

treatment. An important component of pharmacological management is smart polypharmacy, which means stopping unnecessary drugs to minimize drug interactions. Using scheduled drugs rather than prns makes it easier for caregivers to supervise, especially if delirium occurs. In the absence of a 24/7 family caregiver, preventive home care should be considered for monitoring.

Among the most problematic symptoms is fatigue. Fatigue clusters with depression, weakness, anaemia and sleep disturbances. Fatigue, after pain, is the most troubling symptom for elderly cancer patients. There is some evidence that treatment with methylphenidate is helpful once anaemia is corrected and sleep is addressed. Use of erythropoietin for cancer-related anaemia has been only modestly useful for addressing fatigue and carries its own risks if not used according to current guidelines. Compared with middle-aged patients, elderly cancer patients are less likely to suffer with depression and anxiety but more likely to suffer extreme fatigue. Pain management should be addressed following the American Geriatrics Society pain management guidelines. Delirium is markedly underdiagnosed by oncologists, perhaps because it is so common.[33] However, the risk for elderly outpatients is significant if delirium is missed and caregivers and providers need to be vigilant

The numbers of long-term cancer survivors are increasing and the majority, over 4 million in the USA, are of Medicare age. These survivors may be at risk for second cancers or late recurrences. In addition, they may experience late effects of surgery and chemo- and radiation therapy. Several analyses of large databases indicate that elderly cancer survivors continue to have moderately decreased quality of life compared with non-cancer survivors. Late effects include radiation proctitis and cystitis from treatment of prostate and anorectal cancers and sclerosis of the soft tissues of the neck and oral cavity. Lymphoedema can be painful and even with improved surgical techniques continues to impair upper extremity function for breast cancer survivors. Specialized therapies are often necessary. Cognitive impairment due to cancer chemotherapy has been difficult to characterize, most likely because it is multifactorial.[156] However, studies which obtained pretreatment measures indicate that unrecognized cognitive impairment is not uncommon among elderly cancer patients[32] and survivors.[157] Further research is needed to determine whether there are specific phenotypes at greater risk for developing chemotherapy-related cognitive impairment.[158] Patients on hormonal ablation therapies for breast and prostate cancer suffer accelerated ageing, including subtle cognitive impairment, osteoporosis, fractures, falls and adverse changes in cardiac risk factors. Patients who received chest radiation or any of several cardiotoxic chemotherapy agents develop late cardiomyopathies and coronary artery disease. Neuropathies causing pain, denervation and balance problems may persist. For these reasons, it is recommended that cancer survivors have specific care plans so that their primary care physicians can manage their symptoms and risk factors appropriately. The role of exercise interventions, especially among cancer survivors, is under active investigation in several centres. For the elderly cancer survivor, exercise prescriptions should be appropriate to the patient's goals and abilities. On-line resources for medical care of elderly cancer survivors are becoming available. In sum, the best way to maintain function in elderly cancer patients and cancer survivors is to provide good, evidence-based geriatric care.

Key points

- Function is important in planning the management of oncology patients.
- Palliative management improves outcomes.
- Fatigue is an important area to be addressed during chemotherapy.
- Exercise therapy may improve quality of life in cancer patients.

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SECTION 13

Functional Disorders and Rehabilitation

CHAPTER 112

Multidimensional geriatric assessment

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Introduction

The essence of good geriatric practice is the expert management of the medical, psychological and social needs of elderly patients and their family caregivers. For this to be accomplished, the members of the interdisciplinary geriatric team – whether based in a hospital geriatric unit, an outpatient clinic, a nursing home, or a home-care programme – must work closely together to assess carefully the patient's risks and problems and translate this knowledge into care plans that will have far-reaching effects on both the patient's and caregiver's lives.

Such multidimensional assessment implies the detailed investigation of the elderly individual's total situation in terms of physical and mental state, functional status, formal and informal social support and network, and physical environment. This requires the clinician to become involved in collecting, interpreting, synthesizing and weighing a formidable amount of patient-specific information. Much of this differs in kind from the physical symptoms and signs, laboratory values, radiology results and other data that are traditionally combined to reach a medical diagnosis.

Definition

Multidimensional geriatric assessment (MGA) (often called comprehensive geriatric assessment or CGA) is a diagnostic process, usually interdisciplinary, intended to determine an older person's medical, psychosocial, functional and environmental resources, and problems with the objective of developing an overall plan for treatment and long-term follow-up. It differs from the standard medical evaluation in its concentration on older people with their often complex problems, its emphasis on functional status and quality of life (QOL), and its frequent use of interdisciplinary teams and quantitative assessment scales.

As described in this chapter, multidimensional geriatric assessment can vary in its the level of detail, its purpose, and other aspects depending on the clinical circumstances. Therefore, multidimensional assessment denotes both the relatively brief multidimensional screening assessment for preventive purpose in a patient's home as well as the interdisciplinary work-up of a newly hospitalized patient. Despite this broad definition, the term must meet the primary criteria above. For example, a multidimensional evaluation of an older person without link to the overall plan for treatment and follow-up does not meet these criteria. Similarly, a home visit emphasizing psychosocial and environmental factors, but not including a medical evaluation of the older person, is not a multidimensional assessment, since one of the key components of the multidimensionality is not included.

Rationale

While the principles of geriatric assessment may be valid in the treatment of younger persons as well, since bio-psycho-social factors play an important role in medicine for patients of all age groups, there is additional justification for using this multidimensional approach in older persons for various reasons:

– Multi-morbidity and complexity: Many older persons suffer from multiple conditions, and multidimensional assessment helps to deal with these complex situations through its systematic approaches and its setting of priorities.

– Unrecognized problems: Many older persons suffer from problems that have not been reported to the physician or may not even be known to the older person. One of the reasons problems may go undetected is that they may be falsely considered non-modifiable consequences of ageing. Multidimensional geriatric assessment is a method for identifying previously unknown problems.

– Chronic conditions: Many older persons suffer from chronic conditions. Diagnostic information without

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information on functional relevance of the underlying condition is often of limited value for therapeutic decisions or for monitoring follow-up.
– Interaction with social and environmental factors: Once functional impairments or dependencies arise, the older person's condition is strongly influenced by his or her social and physical environment. For example, the arrangement of the older person's in-home environment and the availability of his or her social network might determine whether a person can continue to live in his or her home.
– Functional status: One of the main objectives of medicine for older persons is to prevent or delay the onset of functional status decline. Epidemiological research has shown that functional status decline is related to medical, functional, psychological, social and environmental risk factors. Therefore, both for rehabilitation as well as for prevention the approach of multidimensional assessment helps to take into account potentially modifiable factors in all relevant domains.
– Intervention studies: Multiple intervention studies that compared the effects of programmes based on the concept of multidimensional geriatric assessment with usual care did show benefits of geriatric assessment, including better patient outcomes and more efficient healthcare use.

Brief history of geriatric assessment

The basic concepts of geriatric assessment have evolved over the past 70 years by combining elements of the traditional medical history and physical examination, the social worker assessment, functional evaluation and treatment methods derived from rehabilitation medicine, and psychometric methods derived from the social sciences.

The first published reports of geriatric assessment programmes came from the British geriatrician Marjorie Warren, who initiated the concept of specialized geriatric assessment units during the late 1930s while in charge of a large London infirmary. This infirmary was filled primarily with chronically ill, bedfast and largely neglected elderly patients who had not received proper medical diagnosis or rehabilitation and who were thought to be in need of lifelong institutionalization. Good nursing care kept the patients alive, but the lack of diagnostic assessment and rehabilitation kept them disabled. Through evaluation, mobilization and rehabilitation, Warren was able to get most of the long bedfast patients out of bed and often discharged home. As a result of her experiences, Warren advocated that every elderly patient receive comprehensive assessment and an attempt at rehabilitation before being admitted to a long-term care hospital or nursing home.[1]

Since Warren's work, geriatric assessment has evolved. As geriatric care systems have been developed throughout the world, geriatric assessment programmes have been assigned central roles, usually as focal points for entry into the care systems. Geared to differing local needs and populations, geriatric assessment programmes vary in intensity, structure and function. They can be located in different settings, including acute hospital inpatient units and consultation teams, chronic and rehabilitation hospital units, outpatient and office-based programmes, and home visit outreach programmes. Despite diversity, they share many characteristics. Virtually all programmes provide multidimensional assessment, utilizing specific measurement instruments to quantify functional, psychological and social parameters. Most use interdisciplinary teams to pool expertise and enthusiasm in working toward common goals. Additionally, most programmes attempt to couple their assessments with an intervention, such as rehabilitation, counseling, or placement.

Today, geriatric assessment continues to evolve in response to increased pressures for cost-containment, avoidance of institutional stays, and consumer demands for better care. Geriatric assessment can help achieve improved quality of care and plan cost-effective care. This has generally meant more emphasis on non-institutional programmes and shorter hospital stays. Geriatric assessment teams are well positioned to deliver effective care for elderly persons with limited resources. Geriatricians have long emphasized judicious use of technology, systematic preventive medicine activities, and less institutionalization and hospitalization.

Components of geriatric assessment

A typical geriatric assessment begins with a functional status 'review of systems' that inventories the major domains of functioning.[2–6] The major elements of this review of systems are captured in two commonly used functional status measures – basic activities of daily living (ADL) and instrumental activities of daily living (IADL). Several reliable and valid versions of these measures have been developed, perhaps the most widely used being those by Katz,[7] Lawton[8] and Barthel.[9] These scales are used by clinicians to detect whether the patient has problems performing activities that people must be able to accomplish to survive without help in the community. Basic ADL include self-care activities such as eating, dressing, bathing, transferring and toileting. Patients unable to perform these activities will generally require 12- to 24-hour support by caregivers. Instrumental activities of daily living include heavier housework, going on errands, managing finances and telephoning – activities that are required if the individual is to remain independent in a house or apartment.

To interpret the results of impairments in ADL and IADL, physicians will usually need additional information about the patient's environment and social situation. For example, the amount and type of caregiver support available, the strength of the patient's social network, and the

level of social activities in which the patient participates will all influence the clinical approach taken in managing deficits detected. This information could be obtained by an experienced nurse or social worker. A screen for mobility and fall risk is also extremely helpful in quantifying function and disability, and several observational scales are available.[10,11] An assessment of nutritional status and risk for undernutrition is also important in understanding the extent of impairment and for planning care.[3] Likewise, a screening assessment of vision and hearing will often detect crucial deficits that need to be treated or compensated for.

Two other key pieces of information must always be gathered in the face of functional disability in an elderly person. These are a screen for mental status (cognitive) impairment and a screen for depression.[2,3,6] Of the several validated screening tests for cognitive function, the Folstein Mini-mental State is one of the best because it efficiently tests the major aspects of cognitive functioning.[3,12] Of the various screening tests for geriatric depression, the Yesavage Geriatric Depression Scale,[13] and the Zung Self-Rating Depression Scale[3] are in wide use, and even shorter screening versions are available without significant loss of accuracy.[14]

The major measurable dimensions of geriatric assessment, together with examples of commonly used health status screening scales, are listed in Table 112.1.[2–16] The instruments listed are short, have been carefully tested for reliability and validity, and can be easily administered by virtually any staff person involved with the assessment process. Both observational instruments (e.g. physical examination) and self-report (completed by patient or proxy) are available. Components of them – such as watching a patient walk, turn around and sit down – are routine parts of the geriatric physical examination. Many other kinds of assessment measures exist and can be useful in certain situations. For example, there are several disease-specific measures for stages and levels of dysfunction for patients with specific diseases such as arthritis, dementia and parkinsonism. There are also several brief global assessment instruments that attempt to quantify all dimensions of the assessment in a single form.[17,18] These latter instruments can be useful in community surveys and some research settings but are not detailed enough to be useful in most clinical settings. More comprehensive lists of available instruments can be found by consulting published reviews of health status assessment.[2–6]

Settings of geriatric assessment

A number of factors must be taken into account in deciding where an assessment should take place – whether it is done in the hospital, in an outpatient setting, or in the patient's home. Mental and physical impairment make it difficult for patients to comply with recommendations and to navigate multiple appointments in multiple locations. Functionally impaired elders must depend on families and friends, who risk losing their jobs because of chronic and relentless demands on time and energy and in their roles as caregivers, and who may be elderly themselves. Each separate medical appointment or intervention has a high

Table 112.1 Measurable dimensions of geriatric assessment with examples of specific measures

Dimension	Basic context	Specific examples
Basic ADL	Strengths and limitations in self-care,basic mobility and incontinence	Katz (ADL),[7] Lawton Personal Self-Maintenance Scale,[8] Barthel Index [9]
IADL	Strengths and limitations in shopping cooking, household activities, finances	Lawton (IADL)[8] OARS, IADL Section [3,4]
Social Activities and Supports	Strengths and limitations in social network and community activities	Lubben Social Network Scale[16] OARS, Social Resources Section [3,4]
Mental Health Affective	Degree of anxiety, depression, happiness	Geriatric Depression Scale [12,14] Zung Depression Scale [3]
Mental Health Cognitive	Degree of alertness, orientation concentration, mental task capacity	Folstein Mini-mental State[12] Kahn Mental Status Questionnaire [3,4]
Mobility Gait and Balance	Quantification of gait, balance and risk of falls	Tinetti Mobility Assessment [10] Get up and go test [11]
Nutritional Adequacy	Current nutritional status and risk of malnutrition	Nutritional Screening Checklist [3] Mini-nutritional Assessement [15]
Special Senses	Hearing and vision impairments	Whispered Voice Test or Hearing Handicap Inventory [3–6] Snellen chart or Vision Function Questionnaire [3–6]
Oral Health	Impairments of oral health	Geriatric Oral Health Assessment Index [5,6]

ADL, activities of daily living; IADL, instrumental activities of daily living

time-cost to these caregivers. Patient fatigue during periods of increased illness may require the availability of a bed during the assessment process. Finally, enough physician time and expertise must be available to complete the assessment within the constraints of the setting.

Most geriatric assessments do not require the full range of technology nor the intense monitoring found in the acute care inpatient setting. Yet hospitalization becomes unavoidable if no outpatient setting provides sufficient resources to accomplish the assessment fast enough. A specialized geriatric setting outside an acute hospital ward, such as a day hospital or subacute inpatient geriatric evaluation unit, will provide the easy availability of an interdisciplinary team with the time and expertise to provide needed services efficiently, an adequate level of monitoring, and beds for patients unable to sit or stand for prolonged periods. Inpatient and day hospital assessment programmes have the advantages of intensity, rapidity and ability to care for particularly frail or acutely ill patients. Outpatient programmes are generally cheaper and avoid the necessity of an inpatient stay.

Assessment in the office practice setting

A streamlined approach is usually necessary in the office setting. An important first step is setting priorities among problems for initial evaluation and treatment. The 'best' problem to work on first might be the problem that most bothers a patient or, alternatively, the problem upon which resolution of other problems depends (alcoholism or depression often fall into this category).

The second step in performing a geriatric assessment is to understand the exact nature of the disability through performing a task or symptom analysis. In a non-specialized setting, or when the disability is mild or clear-cut, this may involve only taking a careful history. When the disability is more severe, more detailed assessments by a multidisciplinary or interdisciplinary team may be necessary. For example, a patient may present with difficulty dressing. There are multiple tasks associated with dressing, any one of which might be the stumbling block (e.g. buying clothes, choosing appropriate clothes to put on, remembering to complete the task, buttoning, stretching to put on shirts, or reaching downward to put on shoes). By identifying the exact areas of difficulty, further evaluation can be targeted toward solving the problem.

Once the history has revealed the nature of the disability, a systematic physical examination and ancillary laboratory tests are needed to clarify the cause of the problem. For example, difficulty dressing could be caused by mental status impairment, poor finger mobility, or dysfunction of shoulders, back, or hips. Evaluation by a physical or occupational therapist may be necessary to pinpoint the problem adequately, and evaluation by a social worker may be required to determine the extent of family dysfunction engendered by or contributing to the dependency. Radiological and other laboratory testing may be necessary.

Each abnormality that could cause difficulty dressing suggests different treatments. By understanding the abnormalities that contribute most to the functional disability, the best treatment strategy can be undertaken. Often one disability leads to another – impaired gait may lead to depression or decreased social functioning; and immobility of any cause, even after the cause has been removed, can lead to secondary impairments in performance of daily activities due to deconditioning and loss of musculoskeletal flexibility.

Almost any acute or chronic disease can reduce functioning. Common but easily overlooked causes of dysfunction in elderly people include impaired cognition, impaired special senses (vision, hearing, balance), unstable gait and mobility, poor health habits (alcohol, smoking, lack of exercise), poor nutrition, polypharmacy, incontinence, psychosocial stress and depression. To identify contributing causes of the disability, the physician must thus look for worsening of the patient's chronic diseases, occurrence of a new acute disease, or appearance of one of the common occult diseases listed above. The physician does this through a refocused history guided by the functional disabilities detected and their differential diagnoses, and a focused physical examination. The physical examination always includes, in addition to usual evaluations of the heart, lungs, extremities and neurological function, postural blood pressure, vision and hearing screening, and careful observation of the patient's gait. The mini-mental state examination, already recommended as part of the initial functional status screen, may also determine what parts of the physical examination require particular attention as part of the evaluation of dementia or acute confusion. Finally, basic laboratory testing including a complete blood count and a blood chemistry panel, as well as tests indicated on the basis of specific findings from the history and physical examination, will generally be necessary.

Once the disability and its causes are understood, the best treatments or management strategies for it are often clear. When a reversible cause for the impairment is found, a simple treatment may eliminate or ameliorate the functional disability. When the disability is complex, the physician may need the support of a variety of community or hospital-based resources. In most cases, a strategy for long-term follow-up and often, formal case management should be developed to ensure that needs and services are appropriately matched up and followed through.

Preventive home visits

Preventive home visitation programmes in elderly people are part of national policy in several countries. The

rationale is to delay or prevent functional impairment and subsequent nursing home admissions by primary prevention (e.g. immunization and exercise), secondary prevention (e.g. detection of untreated problems), and tertiary prevention (e.g. improvement of medication use).

This is a typical description of a preventive home visitation programme:[19] 'The assessment included a medical history-taking, a physical examination, haematocrit and glucose measurements in blood samples obtained by finger stick, a dipstick urinalysis and a mail-in faecal occult-blood test. The subjects were also evaluated for functional status, oral health, mental status (presence or absence of depression and cognitive status), gait and balance, medications, percentage of ideal body weight, vision, hearing, extensiveness of social network, quality of social support and safety in the home, and ease of access to the external environment. The nurse practitioners discussed each case with the project geriatricians, developed rank-ordered recommendations, and conducted in-home follow-up visits every three months to monitor the implementation of the recommendations, make additional recommendations if new problems were detected, and facilitate compliance. If additional contact was considered necessary, the nurse practitioner telephoned the participant or was available by telephone. All the participants were encouraged to take an active role in their care and to improve their ability to discuss problems with their physicians. Only in complex situations did the nurse practitioners or study physicians contact the patients' physicians directly.'

Various studies have shown the advantage of the home environment in conducting a multidimensional assessment. The yield of a home visit does not seem to be limited to the preventive application, home visits can also play an important role as part of outpatient or inpatient programmes.

Inpatient geriatric assessment

If referral to a specialized geriatric setting has been chosen, the process of assessment will probably be similar to that described above, except that the greater intensity of resources and the special training of all members of the multidisciplinary team in dealing with geriatric patients and their problems will facilitate carrying out the proposed assessment and plan more quickly, and in greater breadth and detail. In the usual geriatric assessment setting, key disciplines involved include, at a minimum, physicians, social workers, nurses and physical and occupational therapists, and optimally may include other disciplines such as dieticians, pharmacists, ethicists and home-care specialists. Special geriatric expertise among the interdisciplinary team members is crucial.

Geriatric assessment and management programmes were developed for both the acute care and the post-acute care settings. A typical example of an acute care programme is the 'acute care for elderly (ACE) unit', specifically designed for the the special needs of unselected acutely ill elderly inpatients, combining a structured geriatric assessment approach with other adaptations of the process of patient care, such as early discharge planning or interdisciplinary care in the acute care setting for co-existing conditions (e.g. for immobility, confusion, malnutrition).[20] In addition, these units contain specific structural characteristics, for example related to personnel staffing (e.g. additional physical therapists) and environmental adaptations (e.g. rails for the prevention of falls or calendars for better orientation). On the other hand, programmes for the post-acute care setting are focused to in-hospital care of selected older patients who had initial acute care treatment. These programmes admit patients with ongoing need for postacute and rehabilitative care. Typically, these programmes contain a rehabilitation component with an interdisciplinary team assigning patients to specific therapies based on individual geriatric assessment of each patient.[21]

The interdisciplinary team conference, which takes place after most team members have completed their individual assessments, is critical. Most successful trials of geriatric assessment have included such a team conference. By bringing the perspectives of all disciplines together, the team conference generates new ideas, sets priorities, disseminates the full results of the assessment to all those involved in treating the patient, and avoids duplication or incongruity. Development of fully effective teams requires commitment, skill and time as the interdisciplinary team evolves through the 'forming, storming and norming' phases to reach the fully developed 'performing' stage. Involvement of the patient (and carer if appropriate) at some stage is important in maintaining the principle of choice.[22]

Hospital-home assessment programmes

A number of additional published reports have described another multidimensional assessement model in which hospitalized older patients in need of comprehensive assessment are referred to an in-home assessment programme that occurs in their homes following the hospital discharge. The advantages of this approach include shortening the hospital stay, providing the assessment in the home environment that allows evaluation of the home itself and how the patient functions therein, and allowing careful targeting of the in-home assessment to individuals who can derive maximal benefit.

A special approach has been tested in older patients with cardiac risk. In these patients, geriatric assessment in the hospital was combined with a systematic ambulatory follow-up. Early detection of heart failure and optimizing patient adherence with medication prescriptions were key ingredients of these programmes.[23] Several studies

have confirmed that geriatric assessment also reduces unnecessary or inappropriate medications use.

Geriatric assessment in the care of older cancer patients

The International Society of Geriatric Oncology (SIOG) created a task force to review the evidence on the use of a comprehensive geriatric assessment in older cancer patients.[24] Based on a systematic review of the evidence strong evidence was found that a comprehensive geriatric assessment detects many problems missed by a regular assessment in general geriatric and in cancer patients. However, there was corroborative evidence only from a few studies conducted in cancer patients. A recent study confirmed that geriatric assessment conducted in breast cancer survivors is associated with treatment side effects, and long-term survival.[25] Screening tools exist and were successfully used in settings such as the emergency room, but globally were poorly tested. Based on these findings, it was concluded that a comprehensive geriatric assessment, with or without screening, and with follow-up, should be used in older cancer patients, in order to detect unaddressed problems, improve their functional status, and possibly their survival. The task force could not recommend any specific tool or approach above others at this point and general geriatric experience should be used.

Geriatric assessment in the care of nursing home patients

Geriatric assessment is also an important component in the care of older patients in the nursing home. One of the most widely disseminated systems of assessment is the Resident Assessment Instrument.

Effectiveness of geriatric assessment programmes

The pioneering studies of geriatric assessment

A large and still growing literature supports the effectiveness of geriatric assessment programmes (GAPs) in a variety of settings. Early descriptive studies indicated a number of benefits from GAPs such as improved diagnostic accuracy, reduced discharges to nursing homes, increased functional status, and more appropriate medication prescribing. Because they were descriptive studies, without concurrent control patients, they were not able to distinguish the effects of the programmes from simple improvement over time. Nor did these studies look at long-term, or many short-term, outcome benefits. Nonetheless, many of these early studies provided promising results.[2,3,26]

Improved diagnostic accuracy was the most widely described effect of geriatric assessment, most often indicated by substantial numbers of important problems uncovered. Frequencies of new diagnoses found ranged from almost one to more than four per patient. Factors contributing to the improvement of diagnosis in GAPs include the validity of the assessment itself (the capability of a structured search for 'geriatric problems' to find them), the extra measure of time and care taken in the evaluation of the patient (independent of the formal elements of 'the assessment'), and a probable lack of diagnostic attention on the part of referring professionals.

Improved living location on discharge from healthcare setting was demonstrated in several early studies, beginning with TF Williams' classic descriptive pre–post study of an outpatient assessment programme in New York.[27] Of patients referred for nursing home placement in the county, the assessment programme found that only 38% actually needed skilled nursing care, while 23% could return home, and 39% were appropriate for board and care or retirement facilities. Numerous subsequent studies have shown similar improvements in living location.[2,3] Several studies that examined mental or physical functional status of patients before and after comprehensive geriatric assessment coupled with treatment and rehabilitation showed patient improvement on measures of function.[2,3]

Evidence from controlled studies

Beginning in the 1980s, controlled studies appeared that corroborated some of the earlier studies and documented additional benefits such as improved survival, reduced hospital and nursing home utilization, and in some cases, reduced costs.[2,3,28–33] These studies were by no means uniform in their results. Some showed a whole series of dramatic positive effects on function, survival, living location, and costs, while others showed relatively few if any benefits. However, the GAPs being studied were also very different from each other in terms of process of care offered and patient populations accepted. To this day, controlled trials of GAPs continue, and as results accumulate, we are able to understand which aspects contribute to their effectiveness and which do not.

One striking effect confirmed for many GAPs has been a positive impact on survival. Several controlled studies of different basic GAP models demonstrated significantly increased survival, reported in different ways and with varying periods of follow-up. Mortality was reduced for Sepulveda geriatric evaluation unit patients by 50% at one year, and the survival curves of the experimental and control groups still significantly favoured the assessed group at two years.[3,28] Survival was improved by 21% at one year in a Scottish trial of geriatric rehabilitation consultation. Two Canadian consultation trials demonstrated significantly improved six-month survival. Two Danish community-based trials of in-home geriatric assessment

and follow-up demonstrated reduction in mortality, and two Welsh studies of in-home GAPs had beneficial survival effects among patients assessed at home and followed for two years. On the other hand, several other studies of geriatric assessment found no statistically significant survival benefits.[3,31,33]

Multiple studies followed patients longitudinally after the initial assessment and thus were able to examine the longer-term utilization and cost impacts of assessment and treatment. Some studies found an overall reduction in nursing home days. Hospital utilization was examined in several reports. For hospital-based GAPs, the length of hospitalization was obviously affected by the length of the assessment itself. Thus, some programmes appear to prolong initial length of stay while others reduce initial stay. However, studies following patients for at least one year have usually shown reduction in use of acute-care hospital services, even in those programmes with initially prolonged hospital stays.[3,31,33]

Compensatory increases in use of community-based services or home-care agencies might be expected with declines in nursing home placements and use of other institutional services. These increases have been detected in several studies but not in others. Although increased use of formal community services may not always be indicated, it usually is a desirable goal. The fact that several studies did not detect increases in use of home and community services probably reflects the unavailability of community service or referral networks rather than that more of such services were not needed.[3,31,33]

The effects of these programmes on costs and utilization parameters have only seldom been examined comprehensively, due to methodological difficulties in gathering comprehensive utilization and cost data, as well as statistical limitations in comparing highly skewed distributions. The Sepulveda study found that total first-year direct healthcare costs had been reduced due to overall reductions in nursing home and rehospitalization days, despite significantly longer initial hospital stays on the geriatric unit.[28] These savings continued through three years of follow-up. Hendriksen's in-home programme reduced the costs of medical care, apparently through successful early case-finding and referral for preventive intervention.[3,31,33] Williams' outpatient GAP detected reductions in medical care costs due primarily to reductions in hospitalization.[3,31,33] Although it would be reasonable to worry that prolonged survival of frail patients would lead to increased service use and charges, or, of perhaps greater concern, to worry about the quality of the prolonged life, these concerns may be without substance. Indeed, the Sepulveda study demonstrated that a GAP could improve not only survival but prolong high-function survival,[3,28,31,33] while at the same time reducing use of institutional services and costs.

Meta-analytic data

A 1993 meta-analysis attempted to resolve some of the discrepancies between study results, and to try to identify whether particular programme elements were associated with particular benefits.[3,31] This meta-analysis included published data from the 28 controlled trials completed as of that date, involving nearly 10 000 patients, and was also able to include substantial amounts of unpublished data systematically retrieved from many of the studies. The meta-analysis identified five GAP types: hospital units (six studies), hospital consultation teams (eight studies), in-home assessment services (seven studies), outpatient assessment services (four studies), and hospital-home assessment programmes (three studies). The meta-analysis confirmed many of the major reported benefits for many of the individual programme types. These statistically and clinically significant benefits included reduced risk of mortality (by 22 for hospital-based programmes at 12 months, and by 14% for all programmes combined at 12 months), improved likelihood of living at home (by 47% for hospital-based programmes and by 26% for all programmes combined at 12 months), reduced risk of hospital (re)admissions (by 12% for all programmes at study end), greater chance of cognitive improvement (by 47% for all programmes at study end), and greater chance of physical function improvement for patients on hospital units (by 72% for hospital units).

Clearly not all studies showed equivalent effects, and the meta-analysis was able to indicate a number of variables at both the programme and patient levels that tended to distinguish trials with large effects from ones with more limited ones. When examined on the programme level, hospital units and home-visit assessment teams produced the most dramatic benefits, while no major significant benefits in office-based programmes could be confirmed. Programmes that provided hands-on clinical care and/or long-term follow-up were generally able to produce greater positive effects than purely consultative programmes or ones that lacked follow-up. Another factor associated with greater demonstrated benefits, at least in hospital-based programmes, was patient targeting; programmes that selected patients who were at high risk for deterioration yet still had 'rehabilitation potential' generally had stronger results than less selective programmes.

The 1993 meta-analysis confirmed the importance of targeting criteria in producing beneficial outcomes. In particular, when use of explicit targeting criteria for patient selection was included as a covariate, increases in some programme benefits were often found. For example, among the hospital-based GAPs studies, positive effects on physical function and likelihood of living at home at 12 months were associated with studies that excluded patients who were relatively 'too healthy'. A similar effect on physical

function was seen in the institutional studies that excluded persons with relatively poor prognoses. The reason for this effect of targeting on effect size no doubt lies in the ability of careful targeting to concentrate the intervention on patients who can benefit, without diluting the effect with persons too ill or too well to show a measurable improvement.

Since 1993 many new controlled studies on the effects of geriatric assessment programmes have been conducted. However, with principles of geriatric medicine and geriatric asssessment becoming more diffused into usual care, particularly at places where controlled trials are being undertaken, differences between geriatric assessment programmes and control groups seem to be narrowing. Given discrepancies in results between individual trials, several additional meta-analyses and systematic analyses have been conducted over the past few years.[31,33–38]

Assessment in the office practice setting: effects of outpatient geriatric assessment programmes have been less impressive, with a recent meta-analysis showing no favourable effects on mortality outcome.[35] For cost reasons, growth of inpatient units has been slow, despite their proven effectiveness, while outpatient programmes have increased, despite their less impressive effect size in controlled trials. However, some newer trials of outpatient programmes have shown significant benefits in areas not found in earlier outpatient studies, such as functional status, psychological parameters and well-being, which may indicate improvement in the outpatient care models being tested.[3,31,33]

Inpatient geriatric assessment programmes: several meta-analyses on inpatient geriatric assessment studies confirm favourable effects of these programmes on multiple outcomes (e.g. reduction of nursing home admissions and re-admissions to acute care hospital, improvement of functional status outcome), but continue to identify an important heterogeneity in findings and research methodology among published trials. A 2005 meta-analysis confirmed that inpatient comprehensive assessment programmes for older hospital patients may reduce mortality, increase the chances of living at home at one year and improve physical and cognitive function.[34] Two recent meta-analyses conducted separate meta-analyses on inpatient geriatric assessment units, one as part of acute care[36] and one on inpatient geriatric rehabilitation.[21] These two studies, and one additional meta-analysis[37] confirm favourable outcomes, and a large heterogeneity of care processes among these programmes.

Most recently, a 2011 Cochrane meta-analysis concluded that inpatient GAPs increase patients' likelihood of being alive and in their own homes at follow-up, and result in a potential cost reduction compared to general medical care.[38]

Hospital-home assessment programmes: Individual randomized controlled trials evaluated more refined models of hospital-home assessment programmes. For example, Rich *et al*.[23] developed and evaluated the effects of a programme specifically designed for older patients at high risk for recurrent heart failure after hospital discharge. Geriatric assessment was combined with follow-up in the hospital and at home after hospital discharge, and included monitoring of follow-up and compliance adherence. This programme resulted in a reduction of hospital re-admissions, improvement of QOL on participating patients, and in net cost savings.

Preventive home visitation programmes: There is an ongoing debate on the effects of community-based programmes geared towards the prevention of functional status decline and reduction of nursing home admissions among older persons. Meta-analysis of preventive home visits revealed that home visitation programmes are effective if based on multidimensional geriatric assessments with extended follow-up, and if offered to older persons with relatively good function at baseline.[33] Based on a large number of trials, the findings from this meta-analysis indicate that preventive home visitation programmes are effective only if interventions are based on multidimensional geriatric assessment, include multiple follow-up home visits and target persons with relatively good function at baseline. The number needed to visit (NNV) to prevent one admission in programmes with frequent follow-up visits is around 40.

These results have important policy implications. In countries with existing national programmes of preventive home visits, the process and organization of these visits should be reconsidered based on the criteria identified in this meta-analysis. In the United States, a system for functional impairment risk identification and appropriate intervention to prevent or delay functional impairment seems promising. There are a variety of chronic disease management programmes specifically addressing the care needs of the elderly. Engrafting the key concepts of home-based preventive care programmes into these programmes should be feasible, as they continue to evolve, and cost-effective. Identifying risks and dealing with them as an essential component of the care of older persons is central to reducing the emerging burden of disability and improving the QOL in elders.

Conclusion

Published studies of multidimensional geriatric assessment have confirmed its efficacy in many settings. A continuing challenge has been obtaining adequate financing to support adding geriatric assessment services to existing medical care. Despite GAPs' many proven benefits, and their ability to reduce costs documented in controlled trials, healthcare financers have been reluctant to fund geriatric assessment programmes – presumably out of concern that

the programmes might be expanded too fast and that costs for extra diagnostic and therapeutic services might increase out of control. Many practitioners have found ways to 'unbundle' the geriatric assessement process into component services and receive adequate support to fund the entire process. In this continuing time of fiscal restraint, geriatric practitioners must remain constantly creative in order to reach the goal of optimal patient care.

While there is no single optimal blueprint for geriatric assessment, the participation of the multidisciplinary team and the focus on functional status and QOL as major clinical goals are common to all settings. Although the greatest benefits have been found in programmes targeted to the frail subgroup of older persons, a strong case can be made for a continuum of GAPs – screening assessments performed periodically for all older persons and comprehensive assessment targeted to frail and high-risk patients. Clinicians interested in developing these services will do well to heed the experiences of the programmes reviewed here in adapting the principles of geriatric assessment to local resources. Future research is still needed to determine the most effective and efficient methods for performing geriatric assessment and on developing strategies for best matching needs with services.

Key points

- Multidimensional geriatric assessment is an efficient and effective way for evaluating complex elderly patients and planning improved care.
- The process of multidimensional geriatric assessment usually involves the systematic evaluation of function, medical conditions, psychological parameters and social networks through use of an interdisciplinary team and validated assessment measures.
- Multidimensional geriatric assessment has been shown to improve function and survival while reducing healthcare utilization and costs.

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CHAPTER 113

Frailty

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Introduction

Frailty can be defined as that condition when a person loses the ability to carry out important, practiced social activities of daily living when exposed to either psychological or stressful conditions.[1] It should be distinguished from disability. Frailty represents a form of predisability.

Frailty has been objectively defined by Linda Fried and colleagues (Table 113.1).[2,3] Their definition includes weight loss, exhaustion, weakness, walking speed and low physical activity. By this definition, ~6.9% of the older population are frail. Females are more often classified as frail than are males of the same age. Two other similar definitions of frailty that are easier to use in the clinic have been validated[4,5] (Table 113.1). Rockwood *et al*.[6] defined frailty as an increasing number of disabilities. Frailty is the beginning of a cascade that leads to functional deterioration, hospitalization, institutionalization and death (Figure 113.1). Over our lifetime, there is a peak in vitality between 20 and 30 years of age, after which there is a gradual physiological decline in performance (Figure 113.2). This decline can be delayed by positive behaviours such as exercise or accelerated by negative factors such as disease. However, eventually all individuals, if they live long enough, will cross the frailty threshold. This chapter discusses the factors involved in the acceleration of the life slope towards the frailty threshold.

Pathophysiology of frailty

The causes of frailty are multifactorial. The backdrop for the development of frailty is the physiological changes of ageing. The interaction of normal physiology with genes, lifestyle, environment and disease determines which individuals will become frail. In most individuals, frailty is caused by the failure to generate adequate muscle power and/or the failure to have sufficient executive function to utilize the available executive function appropriately. The major causes of frailty are illustrated in Figure 113.3.

Disease

Numerous disease processes can directly or indirectly result in frailty. Many diseases produce an excess of cytokines that can lead to a decrease in muscle mass, food intake and cognitive function. Diseases also lead to a decline in levels of the anabolic hormone testosterone.

Congestive heart failure (CHF) is a condition that is classically associated with frailty. Persons with CHF have a marked decline in their $VO_{2\,max}$, leading to an inability to perform endurance or resistance tasks. Left-sided heart failure leads to intestinal wall oedema. This results in bacterial translocation into the lymphatic and systemic circulation. The bacterial endotoxins (lipopolysaccharides) result in the activation of the immune system and release of cytokines, such as TNF-α. This results in anorexia, loss of muscle mass, weight loss, hypoalbuminaemia and hypocholesterolaemia (Figure 113.4). In CHF, the best predictors of poor outcome are weight loss and hypocholesterolaemia.[7] Activation of the angiotensin II system that leads to cleavage of actomyosin and subsequent clearance of muscle protein by the ubiquitin–proteasome system may also play a role. Angiotensin-converting enzyme inhibitors reverse weight loss and frailty in some persons with CHF.

Persons with chronic obstructive pulmonary disease have a decrease in endurance, weight loss due to poor food intake and increased resting metabolic rate and thermic energy of eating. They lose muscle because of low testosterone levels and increased circulating cytokine levels.

Diabetes mellitus is classically associated with an increase in frailty, injurious falls, disability and premature death (Figure 113.5). Again, the causes are multifactorial and include low testosterone, increased angiotensin II, increased cytokines, peripheral neuropathy, reduced executive function and accelerated atherosclerosis.

Persons with anaemia have reduced endurance, decreased muscle strength, orthostasis, increased falls, increased frailty, decreased mobility, increased disability and increased mortality (Figure 113.6). Both erythropoietin

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Table 113.1 Comparison of three frailty scales.

Cardiovascular Health Study	Study of Osteoporotic Fractures	International Association of Nutrition and Aging
• Weight loss (10 lb in year) • Exhaustion (self-report) • Weakness (grip strength, lowest 20%) • Walking speed (15 ft, slowest 20%) • Low physical activity (kcal per week, lowest 20%)	• Weight loss • Inability to rise from chair five times without using arms • Reduced energy level	• Fatigue • Resistance (climb one flight of stairs) • Aerobic (walk one block) • Illnesses (>5) • Loss of weight (5%)

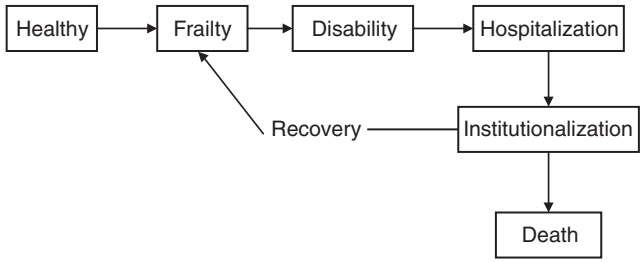

Figure 113.1 The pathway from frailty to death

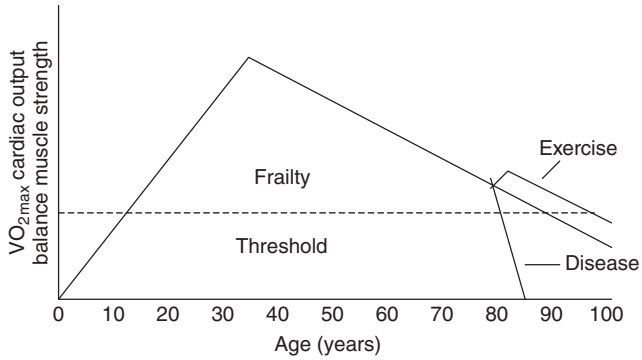

Figure 113.2 The frailty threshold

and darbepoetin-α can reverse the anaemia and many of these changes.[8] The use of these agents has led to a marked increase in the quality of life of patients with chronic kidney failure, anaemia of chronic disease and myelofibrosis.

Polymyalgia rheumatica results in painful muscles with proximal myopathy. The diagnosis is confirmed by finding an elevated erythrocyte sedimentation rate. Treatment of this condition with corticosteroids reverses the frailty that it produces. Unfortunately, this totally reversible condition is often misdiagnosed by clinicians.

Endocrine disorders, such as hyperthyroidism, hypothyroidism and hypoadrenalism, can have insidious onset. Joint pain, that is, the arthritides, is classically associated with immobility. Immobility, over time, leads to loss of muscle mass and power and to a decline in endurance, the hallmarks of frailty. Pain can further induce frailty secondarily to increasing depression in older persons.

Decreased food intake

Older persons develop a physiological anorexia of ageing that is associated with a loss of weight. The causes of the anorexia of ageing are multifactorial.[9] Social causes, such as isolation and dysphoria, and the decline in smell and increase in taste threshold are obvious causes. Recently, there have been a number of studies that demonstrated that decreased compliance and adaptive relaxation of the stomach result in a more rapid antral filling and early satiety. Excess production of cholecystokinin from the duodenum in response to a fatty meal is another cause of anorexia in older persons. High circulating cytokine levels in older persons have been associated with anorexia. Males have a greater decrease in both absolute and relative amounts of food intake over the lifespan. This appears to be due to the fall in testosterone, which results in an increase in leptin levels and, therefore, greater anorexia.

In addition to the physiological anorexia of ageing, many reversible causes of anorexia occur in older persons. These are easily remembered by the mnemonic MEALS-ON-WHEELS (Table 113.2).

Sarcopenia

Sarcopenia is the excessive loss of muscle mass that occurs in older persons.[10–12] It is usually defined as a greater than two standard deviations amount of lean tissue compared with that of younger persons. It occurs in 13–24% of persons aged 60–70 years and in about 50% aged over 80 years. The best measure of sarcopenia is based on the appendicular skeletal mass as measured by dual-energy X-ray absorptiometry (DEXA), divided by the height in metres squared. It can also be calculated using magnetic resonance imaging (MRI), computed tomography (CT) or bioelectrical impedance. DEXA and MRI measures are highly correlated. Ultrasound is proving to be an excellent

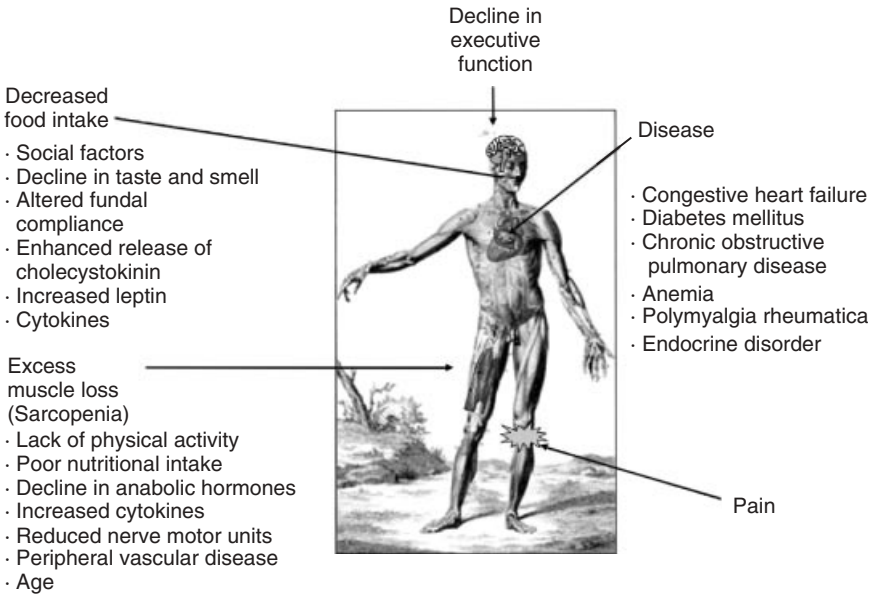

Figure 113.3 The major causes of frailty

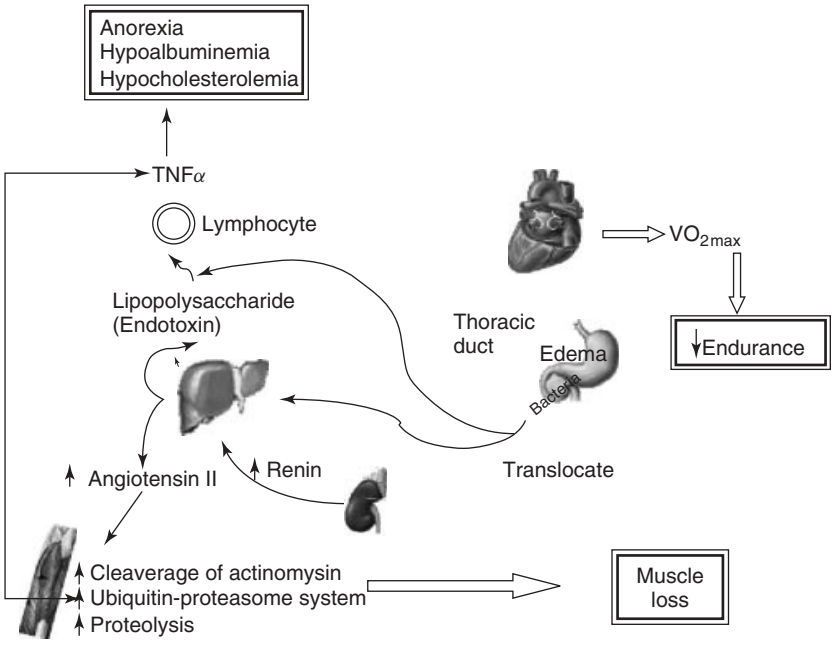

Figure 113.4 The pathogenesis of frailty in congestive heart failure

measure of muscle mass loss in older persons.[13] Sarcopenia is strongly correlated with disability. Most sarcopenic individuals have also lost fat. However, a subset of individuals remain fat while losing muscle mass. These individuals have been characterized as the 'sarcopenic obese' or the 'fat frail'. Longitudinally, those with obese sarcopenia have been found to be the most likely to develop future disability and mortality.[14] Myosteatosis – the infiltration of fat into muscle – appears to be a separate condition related to insulin resistance. Mitochondrial failure or elevated circulating triglycerides lead to the accumulation of triglycerides within the cell. This alters the function of the insulin receptor substrate and, therefore, the GLUT transporter, leading to insulin resistance.

The development of sarcopenia and its effect on frailty have been characterized in the worm *Caenorhabditis elegans*. In *C. elegans*, muscle deterioration (sarcopenia) with ageing leads to a decline in body movement. The muscle deterioration also correlates with behaviour deficits (a frailty equivalent). These changes rarely correlated with a decreased lifespan. Mutations in daf-2 (the worm's IGF-1) delay these changes.

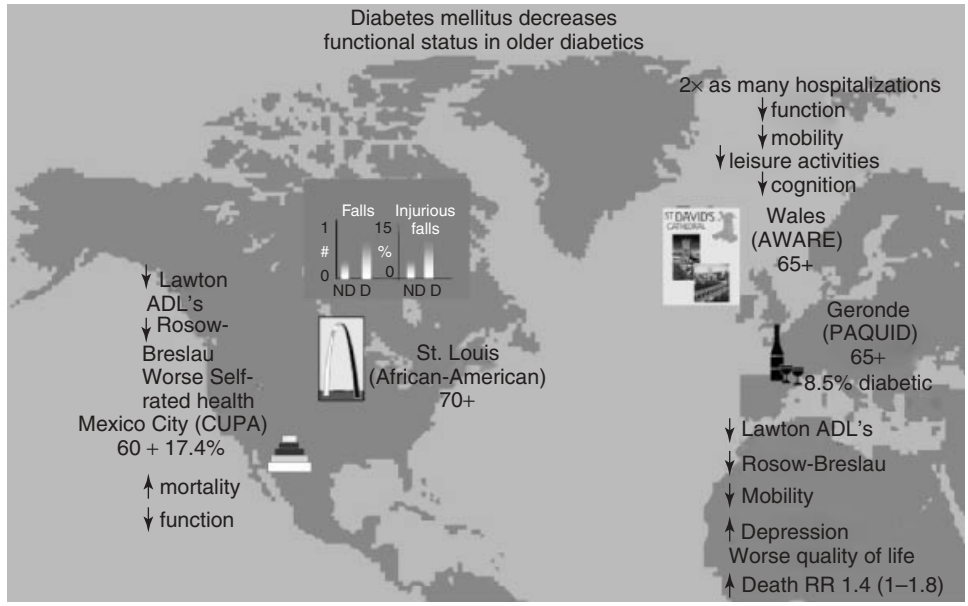

Figure 113.5 Frailty and diabetes mellitus

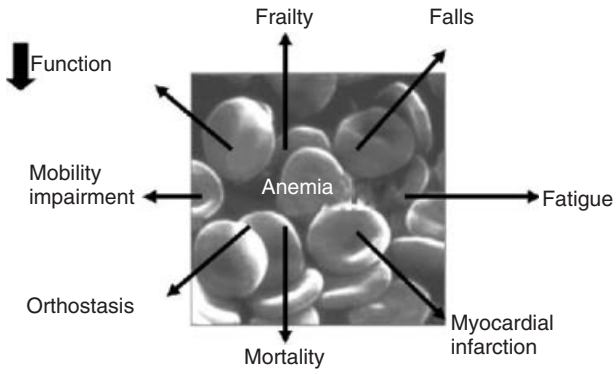

Figure 113.6 Frailty and anaemia

Table 113.2 MEALS-ON-WHEELS mnemonic for treatable causes of weight loss.

Medications (e.g. digoxin, theophylline, cimetidine)
Emotional (e.g. depression)
Alcoholism, elder abuse, anorexia tardive
Late-life paranoia
Swallowing problems
Oral factors
Nosocomial infections (e.g. tuberculosis)
Wandering and other dementia-related factors
Hyperthyroidism, hypercalcaemia, hypoadrenalism
Enteral problems (e.g. gluten enteropathy)
Eating problems
Low salt, low cholesterol and other therapeutic diets
Stones (cholecystitis)

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There is evidence that sarcopenia originates at birth. In the Hertfordshire cohort study, it was shown that grip strength correlates with birth weight. Genetic studies have shown that persons with a single I or double I allele for angiotensin-converting enzyme appear to be able to generate more power when exercising regularly than those with D allele. Epidemiological studies have suggested that the best predictors of muscle mass and strength in older persons are age, energy intake, physical activity, IGF-1, testosterone and cytokines.[15] Hypovitamin D is also associated with decreased muscle strength and falls.[16]

Testosterone levels decline at the rate of 1% per year from the age of 30 years in men and rapidly between 20 and 40 years in women.[17,18] Testosterone inhibits the movement of pluripotential stem cells into the fat cell lineage and stimulates the muscle cell lineage to result in the production of satellite cells. Satellite cells are essential for the repair of skeletal muscle.[19] Testosterone also stimulates muscle protein synthesis and inhibits the ubiquitin–proteasome pathway, resulting in a decrease in muscle protein turnover. Testosterone replacement, even in non-hypogonadal males, increases muscle mass.[20] Pharmacological doses of testosterone or testosterone replacement in hypogonadal males lead to an increase in muscle strength and muscle power.[21] These changes have now been shown to lead to functional improvement. However, there is a small amount of evidence that testosterone has similar effects in older women.

Three studies in older persons with frailty have shown some functional improvement.[22–24] An important side effect is oedema. More persons died in the placebo arms of these studies than in the testosterone treatment arms. Similarly, testosterone treatment has improved function in older persons with heart failure.[25]

A number of selective androgen receptor molecules (SARMs) are being developed, in an attempt to find androgenic compounds that have a specific effect on muscle but are less likely to produce side effects (Table 113.3). Ostarine is a SARM that increases muscle mass and power performance in older persons. Dehydroepiandrosterone (DHEA), a weak androgen, failed to produce an effect on muscle strength or muscle mass when given at 50 mg daily for 1 year to 288 men and women.

Another anabolic hormone, growth hormone, increases muscle mass but not strength in older persons.[26] The effect of growth hormone is predominantly on type II muscle fibres. Ghrelin, a growth hormone secretagogue produced in the fundus of the stomach, also appears to increase muscle mass.

Table 113.3 Selective androgen receptor molecules.

Steroids
Nandrolone
Oxymethalone
Oxandrolone
Non-steroidal
2-Quinoline
Coumarin
Phthalimide
Bicalutamide
Acetothiolutamide

Insulin growth factor (IGF) is produced in three alternative forms in muscle. One of these forms, a mechanogrowth factor (MGF), is produced in response to mechanical overload.[27] The ability of MGF to be produced in response to mechanical overload declines with ageing. Resistance exercise increases MGF in human quadriceps and this increase is greater when growth hormone is also given. IGF enhances satellite cell production. Localized

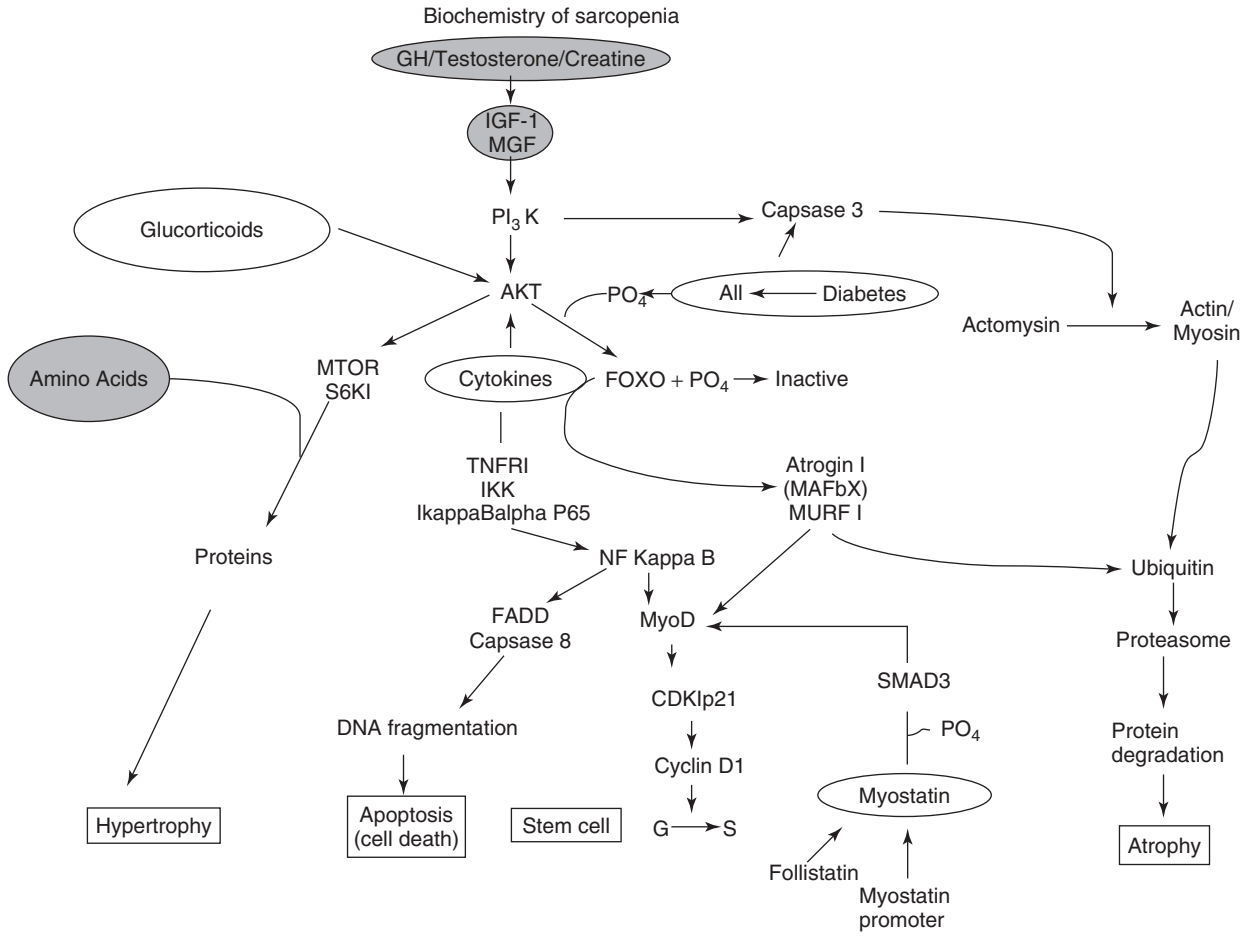

Figure 113.7 Schematic view of the biochemistry of sarcopenia

IGF transgene expression sustains hypertrophy and regeneration of senescent skeletal muscle.[28]

Myostatin D inhibits muscle growth. A double deletion of myostatin D in mice leads to muscle hypertrophy, a veritable 'mighty mouse'. Double deletions of myostatin D in cows, whippets and in a single human result in marked muscle hypertrophy.[29] Myostatin produces its effect through the activin II receptors. A soluble circulating the activin IIb receptor can scavenge activan and lead to muscle and bone hypertrophy in rodents, monkeys and humans.[30]

Motor unit functioning is essential for the maintenance of muscle function. The motor unit firing rate is significantly decreased in the old-old, that is, those over 80 years of age. Ciliary neurotrophic factor (CNTF) levels decline with age and this decline correlates with the decrease in muscle strength with ageing. Administration of CNTF leads to a twofold increase in soleus muscle size.

Cytokines are soluble peptide messengers that are synthesized by white cells, neuronal cells and adipocytes. Excess of TNF-α and interleukin-6 leads to loss of muscle strength. High levels of C-reactive protein and interleukin-6 are associated with a decrease in handgrip strength and in physical performance.[31]

Elevated homocysteine levels and peripheral vascular disease lead to poor blood flow to muscles, with muscle atrophy and decreased function. Creatine is an essential amino acid for muscle. Creatine, together with exercise, may improve muscle performance in older persons.[32]

In the end, the development of sarcopenia depends on an imbalance of the normal everyday renewal cycle of muscle. There is either an excess of atrophy and apoptosis or a diminution of hypertrophy and satellite cell production. Figure 113.7 provides a schematic view of the biochemistry of sarcopenia.

Conclusion

Frailty is a predisability state. It is been defined objectively. The causes of frailty are multifactorial. Frailty can have a single cause, such as anaemia. Reversal of the anaemia with iron, folate, vitamin B_{12} or erythropoietin will, in this case, reverse frailty. In other cases, frailty is due to the interplay of hormones and cytokines with disease processes and poor-quality nutritional intake. In these cases, the management of frailty requires a careful assessment of the causative factors and a multifaceted treatment regimen. One approach to the preventive strategies necessary to slow the onset of frailty is given in Table 113.4.

Table 113.4 Preventive strategies to slow the onset of frailty.

Food intake maintenance
Resistance exercises
Atherosclerosis prevention
Isolation avoidance (i.e. depression)
Limit pain
Tai Chi and other balance exercises
Yearly check for testosterone deficiency

Key points

- Frailty is predisability and has been objectively defined.
- Frail persons are precipitated into disability by experiencing a stressful event.
- Causes of frailty include chronic diseases, pain, poor-quality nutritional intake, impaired executive function and sarcopenia.
- The interplay of hormones and cytokines is an important determinant of frailty.

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CHAPTER 114

Rehabilitation

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Introduction

The human and economic consequences of avoidable dependency in older people are considerable. This reality was first stated by Marjorie Warren over 60 years ago when she emphasized the need to help sick elderly people to regain their functional independence, the primary elements of which are mobility and independent self-care.[1]

Older people who typically benefit from rehabilitation will have had a disabling event of recent onset. This is commonly an age-related event such as a stroke, hip fracture, other fall-related injury or deconditioning following a major illness. Many elderly people will have ongoing limitations from other diseases such as osteoarthritis or Parkinson's disease.

Though there are many reasons why rehabilitation in the old differs from that in the young, perhaps the greatest is the lack of physiological reserve with which to combat a disabling insult. As a consequence, recovery is typically prolonged and the pre-morbid functional state is never fully regained. The specific diseases to which elderly people are susceptible are described throughout this text. This chapter focuses on the process of optimizing recovery from the major disabling diseases of old age and on strategies for adaptation to their long-term sequelae.

Terminology and classifications

For many years, the World Health Organization (WHO) has sought to classify aspects of health and disease, most notably through its International Classification of Disease, now in its tenth revision (ICD-10).[2] Such systems provide a standard language and framework for the description of health and health-related states across geographical boundaries, disciplines and sciences.

To complement the ICD, in 1980 the WHO introduced its International Classification of Impairments, Disabilities and Handicaps (ICIDH).[3] This stated that any illness could be considered at three levels: impairment, disability and handicap. In simple terms, *impairment* refers to the pathological process affecting the person, *disability* to the resulting loss of function, and *handicap* to any consequent reduction in that individual's role in society.

The ICIDH had significant limitations, including the use of pejorative terms that emphasized the negative consequences of ill health and played down its social and societal dimensions. Consequently, in 2001, WHO produced a revised classification, the International Classification of Functioning, Disability and Health (ICF), which challenged traditional views on health and disability and allowed positive experiences to be described. In particular, the ICF focuses on the impact of the social and physical environment on a person's functioning.

The ICF contains two *parts*, each with two *components*:

Part 1 Functioning and Disability
- (a) Body Functions and Structures
- (b) Activities and Participation

Part 2 Contextual Factors
- (c) Environmental Factors
- (d) Personal Factors

Under this classification, each component is further divided into various *domains* and each domain into a number of *categories*, which form the units of classification.

The ICF has the following definitions:

Impairment: problems in body function or structure such as a significant deviation or loss.

Activity: the execution of a task or action by an individual.

Activity limitations: difficulties an individual might have in executing activities.

Participation: involvement in a life situation.

Participation restrictions: problems an individual may experience in involvement in life situations.

Environmental factors: the physical, social and attitudinal environment in which people live and conduct their lives.

Components of the ICF can be expressed in both positive and negative terms. Thus, *functioning* is an umbrella term for all body functions, activities and participation while

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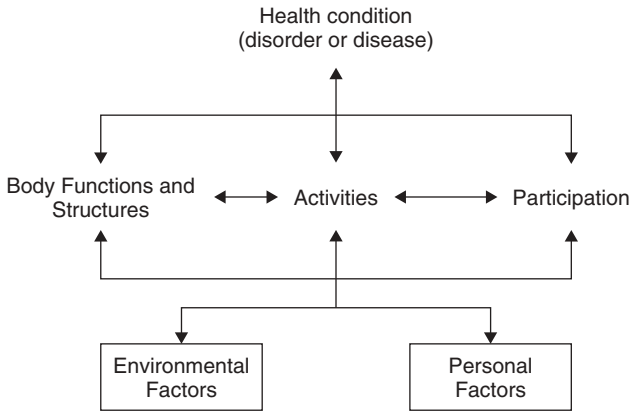

Figure 114.1 The complex interaction between health status, activity and participation.

disability is a collective term for impairments, activity limitations or participation restrictions.

As illustrated by Figure 114.1, an individual's functioning is a result of a complex interaction between the health condition and contextual factors (i.e. environmental and personal factors). Their interaction is highly dynamic such that any intervention in one area might impact on the other, perhaps in unpredictable ways.

Consider, for example, an individual with Parkinson's disease, whose impairment (problems in body function or structure) is described elsewhere in this text. As a consequence, the person may have some activity limitations such as difficulty with personal care and mobility. In turn, the person cannot pursue former hobbies and interests (participation restriction), restrictions that might be exacerbated if widowed and living alone in a first floor apartment. Now suppose that she falls and fractures her hip. This new impairment causes her to lose confidence. Further restrictions in activity and participation ensue and she becomes even more isolated, withdrawn and depressed. The feedback loops shown in Figure 114.1 indicate how vicious cycles can develop with the person's level of activity and participation spiralling downwards.

Simply stated, rehabilitation is a process that seeks to minimize activity and participation restrictions resulting from impairment. Many and more comprehensive definitions exist; perhaps the most widely accepted is the UN definition:[5]

> Rehabilitation means a goal-orientated and time-limited process aimed at enabling an impaired person to reach an optimum mental, physical and/or social functional level, thus providing him or her with the tools to change his or her own life. It can involve measures intended to compensate for a loss of function or a functional limitation (for example the use of technical aids) and other measures intended to facilitate social adjustment or readjustment.

Figure 114.1 also illustrates how rehabilitation programmes can impact at various points in the impairment-activity-participation cycle. Not only can they prevent the progression of impairment to activity restriction and of activity restriction to participation restriction, they can also prevent further impairments and the development of vicious cycles.

Determinants of activity and participation restrictions

As summarized in Table 114.1, many factors determine the activity and participation restrictions that result from a given impairment. The type of impairment is of paramount importance, with some diseases being inherently more likely to cause restrictions than others. The site of a pathological lesion is also important as is well illustrated by stroke disease, where large lesions in some parts of the brain may be asymptomatic while smaller lesions in strategic areas may cause major problems.

Older patients often have pre-existing impairments contributing to activity and participation restrictions and rehabilitation programmes can be influenced as much by these as by any new impairments.

Regarding reduced physiological reserve, the ageing process is characterized by a gradual functional decline in most bodily systems – a phenomenon which tends to be unimportant when organs and physiological systems are 'at rest' but is often critical when they are placed under stress by a disabling illness or event. However, it must be emphasized that even very old people can recover from major illness

Table 114.1 Determinants of activity and participation restrictions.

Determinants of activity restriction
Type of impairment (nature and severity of the disease process)
Presence of associated impairments
Degree of physiological reserve
Level of physical fitness
Determinants of participation restriction
Intrinsic factors
Attitude
Personality
Ability to adjust
Cultural issues
Extrinsic factors
Financial resources
Housing
Other resources
Social supports (spouse, family, neighbours, friends, pets)

and failure to make progress at rehabilitation can seldom be attributed to reduced physiological reserve alone. Of far greater importance is the lack of activity and physical fitness that typifies elderly people in modern societies.[6] Many of today's older people grew up in an era when exercise was not encouraged and sports and recreation facilities were relatively inaccessible. An age-related decline in muscle mass (sarcopenia) and strength is aggravated by physical inactivity[7] and numerous studies have shown an association between sarcopenia and activity restriction.[8]

Such age-associated phenomena are reversible. For example, weight training increases muscle strength in older people and improves functional capacity[9] and older people who participate in lifelong aerobic or strength training have comparable muscle strength to sedentary middle-aged individuals.[10] Although there is little data on the relationship between prior physical fitness and recovery from impairment, it is probable that those who are physically unfit have worse outcomes.

The degree of participation restriction resulting from activity restriction is influenced by several intrinsic and extrinsic factors (Table 114.1). Intrinsic factors include the person's attitude in adjusting to activity restriction. Somebody who suffers a functional loss typically experiences a grief-like reaction. Some demonstrate better coping strategies than others; they are more positive in their approach, assume greater control of their situation and find solutions to their problems. These issues are discussed in more detail later.

Extrinsic factors that impact on participation include the available resources and supports in dealing with activity restriction. In societies where health and welfare systems are poorly developed, personal finance is required for the many components of a rehabilitation programme. These include the provision of physical therapy, prosthetic devices, home modification and ongoing care. Of even greater importance are the social supports on which the person can rely at all stages of the rehabilitation programme, and particularly upon returning to their former environment. In this regard elderly females are particular disadvantaged, often being widowed and living alone. In Australia, for example, 20% of people aged 65 years and over and 27% of elderly people with activity restriction live alone.[11] In recent decades, other demographic trends, such as the loss of the nuclear family and the recruitment of informal carers into paid employment have further reduced the supports available to elderly people.

Psychological aspects of rehabilitation

The onset of impairment, particularly if unexpected or catastrophic, is generally associated with some emotional disturbance. Expected feelings include a sense of loss with regard to one's physical or mental faculties, to relationships with others or to inanimate objects such as one's home or other possessions. A typical grief reaction involves phases of denial, anger and depression leading to enough acceptance to allow a relatively normal life to be resumed. However, adjustment to impairment is sometimes abnormal. For example, over 40% of older people become depressed following a myocardial infarction and this worsens the prognosis.[12] High levels of depression have also been found following stroke,[13,14] despite participation in a rehabilitation programme.[15]

Some are inherently more adaptable and optimistic than others when faced with an impairment and this greatly influences the development of activity and participation restriction. At one end of the spectrum of responses are 'highly motivated' people who set ambitious goals and work hard to achieve them. At the other end are those who submit to their impairment, disengage, surrender power and autonomy and adopt the 'sick role'.

There are psychological theories to explain such different responses, such as that proposed by Kemp,[16] who contends that motivation is a dynamic process driven by four elements: the individual's wants, beliefs, the rewards to achievement, and the cost to the patient. The first three elements drive motivation in one direction and this is counteracted by the cost in terms of pain and effort. Thus, if a person really wants something, believes it to be attainable and potentially rewarding, he will strive to achieve it, provided the cost is acceptable. The converse also holds. Using this framework, the rehabilitation specialist can help individuals by setting goals, challenging incorrect beliefs, establishing rewards and minimizing the physical and mental cost of the rehabilitation process (cf. section on Psychosocial Support).

Principles of rehabilitation

The principles of rehabilitation are broadly similar irrespective of the underlying problem and of the working environment. *Early intervention* is crucial, as avoidable activity and participation restriction can occur soon after the onset of impairment. Problems should be anticipated and avoided as once established, they may prove irremediable. For example, a person with a flaccid hemiplegia is at risk of shoulder subluxation and its long-term sequelae. Proper handling and limb positioning in the immediate post-stroke period will minimize this risk.

A *team approach* is also essential. A properly resourced team will have input from medical and nursing staff, physiotherapists, occupational therapists, speech pathologists, clinical psychologists, dieticians and social workers. Doctors are primarily concerned with the assessment and management of impairment while remedial therapists are skilled in managing activity restriction and social workers in managing participation restriction. Nursing staff have an

holistic brief with areas of expertise capable of influencing both activity and participation restriction.

To function effectively, team members need to communicate with each another. When they are co-located (e.g. in a designated rehabilitation unit), exchange of information occurs regularly and informally. Most teams also have regular formal meetings to discuss the progress of patients, to revise goals, plan discharge and organize follow-up in the community.

The rehabilitation process

The steps in any rehabilitation process are summarized in Table 114.2. Though presented in chronological order, in practice there is considerable overlap between the elements, many of which occur simultaneously and some of which must be regularly revisited. For example, while the assessment of a patient's impairment, activity and participation restriction is an important initial step, this needs to be repeated frequently (at least weekly) as the rehabilitation programme proceeds.

Assessment

It is essential that patients be assessed before entry into a rehabilitation programme to ensure that their problems are remediable and to determine their optimal management. The selection of patients for rehabilitation can be difficult as it is unfair to subject a person who cannot benefit to a demanding programme and in the process to raise false expectations and waste resources. On the other hand, those who can benefit even to a limited extent should not be denied access.

Assessment should focus on both the problem in the individual and the individual with the problem. The nature and severity of all impairments, whether new or long-standing, should be determined. It is essential to obtain a baseline measure of functional status, so that progress can be monitored and the efficacy of rehabilitation reviewed. A variety of assessment tools are available, ranging from simple subjective measures to the more complex and time consuming. The best choice of tool depends on the clinical context. Busy clinicians can often estimate the extent of activity and participation restriction by asking a few simple questions and by making some equally simple observations. Detailed assessment of activity and participation restrictions using standardized scales is generally left to remedial therapists and social workers.

Table 114.2 Steps in the rehabilitation process.

1 Assessment
2 Setting goals
3 Therapy
4 Aids and adaptations
5 Education
6 Psychological support
7 Evaluation
8 Follow-up

Assessment of activity and activity restriction

Assessment begins with the clinical history. For the person with a recent impairment, it is important to determine the premorbid as well as the current functional status. A common approach is to focus on activities of daily living (ADLs). These are classified as items of personal care (e.g. washing, grooming, dressing, using toilet, eating, etc.) and those involving the use of 'instruments' – hence known as instrumental ADLs (IADLs). The latter include such tasks as preparing meals, using the telephone, doing laundry and other housework, gardening, shopping and using public transport. If any difficulties are reported, it is important to determine how the person manages. Are these tasks neglected or do others provide help?

More formal, objective and standardized assessment of activity restriction is generally required when patients are entering a rehabilitation programme. Several assessment scales exist and their strengths and weaknesses have been analysed.[17] As yet, there is no consensus on the best assessment scales and a lack of uniformity inhibits comparative research.

The education literature provides a model drawn to explain the difficulty in reaching such a consensus.[18] This contends that the utility (U) of any assessment tool is governed by the formula:

$$U = \frac{V \times R \times A}{C}$$

where V = validity; R = reliability; A = acceptability and C = cost. While the ideal tool will score highly in the first three areas and be low on cost, in practice, assessment tools with high validity and reliability are invariably costly (i.e. resource intensive) and/or have low acceptability (e.g. are intrusive). The converse is equally true; tools that are easy and cheap to administer often have poor validity and reliability. The multiplication factor in the equation is important, because if any one element of the equation is close to zero, then the overall utility of the assessment tool will also be close to zero. In practice, the utility of any assessment tool is a trade-off between these elements.

Despite these considerations, the UK's Royal College of Physicians and British Geriatrics Society jointly endorse a number of standardized functional assessment scales for elderly patients, all of which have stood the test of time (Table 114.3). Collectively, they assess competence with activities of daily living, vision, hearing, communication, cognitive function and memory, depression and quality of life.[27]

Table 114.3 Standardized functional assessment scales for elderly patients.

Domain assessed	Recommended scale	Comments
Basic activities of daily living (ADL)	Barthel Index[19,20]	Observation of what the patient *does*. Ceiling effect in ambulatory patients.
Vision, Hearing, Communication	Lambeth Disability Screening Questionnaire[21]	Postal questionnaire
Memory and Cognitive Function	Abbreviated Mental Test (AMT)[22,23]	10 questions from longer Roth-Hopkins test
Depression	Geriatric Depression Scale[24]	Screening test with 30 questions; 15 questions in short form[25]
Subjective morale	Philadelphia Geriatric Center Morale Scale[26]	Distinct from depression, although some overlap

Reproduced from Royal College of Physicians and British Geriatrics Society Joint Workshops (1992), [27] with permission.

Such standardized scales facilitate the exchange of information across acute, rehabilitation and community-based healthcare settings. They allow the effectiveness of rehabilitation to be measured and foster comparisons of different approaches to treatment. Standardized assessments can also minimize the repeated gathering of identical information by the various members of multidisciplinary rehabilitation teams.

Other assessment scales deserve special consideration. Neurodegenerative disorders are common in older patients and Wade has provided a valuable reference for commonly used assessment measures in neurological rehabilitation.[28] A drive towards output-driven health funding in many countries has stimulated the development of specific outcome measures in rehabilitation. The Functional Independence Measure (FIM) scores patient progress in 18 common functions concerning self-care, sphincter control, mobility, locomotion, communication and social cognition.[29] Attempts have been made to use the FIM to identify the most effective and efficient aspects of rehabilitation programmes.[30,31]

Assessment of participation and participation restriction

As individuals uniquely interact with their environment, so any reduced role in society (participation restriction) resulting from activity restriction will be unique to the individual. Furthermore, it is possible for somebody to develop major participation restriction in one area and have little or no restriction in another. Thus, the person who loses mobility following a lower limb amputation may no longer be able to play golf but can continue to drive a car. As explained earlier, the level of participation restriction is mainly determined by one's ability to adapt. While some fail in this regard, for others the onset of activity restriction prompts a redefinition rather than a loss of social role. Potential losses in one area can be offset by gains elsewhere, thus minimizing participation restriction. The authors occasionally encounter people who consider their lives to have been enriched through developing an impairment and associated activity restriction.

It follows that an assessment of participation restriction can only be obtained through gaining an in-depth understanding of the individual and the manner in which he or she has come to terms with activity restriction. Such measurements are always subjective. They are also unstable over time and can be influenced by psycho-behavioural variables such as mood. For these reasons the assessment of participation restriction is largely neglected in both clinical and research settings.

Goal setting

Assessment should culminate in the setting of rehabilitation goals. To avoid frustration and disappointment for all concerned, goals should be realistic and take account of the individual's impairment and pre-morbid functional status. It is sometimes appropriate to set modest goals, such as helping an amputee patient to become wheelchair-independent rather than to walk. It is essential that all multidisciplinary team members, and particularly the patient, are involved in setting goals and that there is general agreement on the validity of the set targets.[32] A programme can be seriously compromised if key people differ on what each is trying to achieve. Patients with ambitious goals seem to make greater progress than those with more modest targets;[33] a pragmatic approach is to set ambitious but achievable goals.

Short-term (intermediate) as well as long-term (final) goals should be identified; by achieving a succession of intermediate goals, the patient arrives at the final goal. It is important to set realistic time frames for the achievement of goals, bearing in mind that the rate of progress can be difficult to predict, particularly at the outset. Goals and time frames should therefore be flexible, be regularly reviewed and modified when necessary.

Therapy

A detailed description of the role of the various multidisciplinary rehabilitation team members is outside the scope of this chapter. In brief, doctors focus on the identification and management of the presenting problem and coexisting impairments. Underlying risk factors are identified and minimized; potential complications are anticipated and prevented. Thus, in an arteriopath who has had an embolic stroke, the doctor monitors anticoagulation, controls hypertension and manages coexisting angina pectoris and diabetes mellitus. Occupational therapists (OTs) assess and enhance competence with activities of daily living. Physiotherapists provide therapies that target specific problems and enhance cardiorespiratory, neuromuscular and locomotor function. Speech and Language Therapists deal with communication issues and swallowing disorders. In specific situation, input from other health professionals (e.g. clinical psychologists, podiatrists, dieticians) may be invaluable.

Aids and adaptations

The use of aids has the potential to reduce activity and participation restriction for many impaired people. Devices range from the simple and inexpensive to the technologically advanced. They help people in diverse ways, from carrying out activities of daily living to the maintenance of mobility and the promotion of continence. The most commonly used aids have been critiqued by Mulley.[34] The provision of an aid is not always the best option for an impaired person as it can foster dependence rather than independence. However, those in real need often do not avail of even basic and aids and appliances.[35]

Advice on the suitability of aids is best left to OTs or others with particular expertise. Physiotherapists can advise on mobility aids, speech therapists on communication aids, audiologists on hearing aids and continence advisors on continence aids. Such people can also provide follow-up and ensure that aids are properly used and maintained and continue to serve their purpose.

The design, construction and fitting of prostheses (devices which replace body parts) and orthoses (devices applied to the external surface of the body to provide support, improve function, or restrict or promote movement) require particular skill and technological expertise. Well-resourced rehabilitation centres have access to prosthetists and orthotists as part of the multidisciplinary team.

Adapting the home environment also promotes activity and participation. This might include the installation of simple handrails or ramps, or improving access to shower and toilet areas. Early input from an OT, often including a home visit, ensures that modifications will be appropriate and timed to facilitate hospital discharge.

Education and secondary prevention

Education is a vital part of rehabilitation, as it empowers the patient to minimize the activity and participation restrictions that result from impairment. The unique educational needs (in terms of knowledge, skills and attitudes) of the individual must first be determined and the patient has a central role in setting the agenda. A compromise must be reached when there is a discrepancy between the person's perceived needs and actual needs (as determined by health professionals).

Generally, patients need to learn about their impairment, its aetiology, underlying risk factors, management and prognosis. This fosters compliance with treatment and impacts on attitudes. The skills required will be highly specific and can range from cognitive skills to the more practical manual skills. Patients who are empowered through education are more likely to assume responsibility for their health and to institute life changes to maintain it.

Education should be integrated into all stages of the rehabilitation programme through informal daily contact with team members. Formal educational activities can complement the more informal. These can occur on an individual basis or in group settings. The format can vary from the distribution of educational literature to didactic presentations and small group discussions. Discussion groups allow patients to learn from one another and provide mutual support and encouragement.

Psychosocial support

Rehabilitation team members should have at least a basic understanding of those common psychological issues which impact on the rehabilitation process. These include the physiology of grief and loss and the psychology of motivation. They need practical skills in helping patients to mentally and physically adjust to their loss. To this end, they need to get to know and understand the patient, and especially his or her beliefs, goals and fears. This calls for good communication skills and particularly good listening skills. People tend to fear the unknown; an explanation of their condition and the rehabilitation process helps to reduce anxiety. Some will be as concerned about potential future problems (e.g. the risk of a further stroke) as about the immediate one. If such concerns do not surface spontaneously, they should be sought and discussed.

Regular reassurance and positive feedback are simple and effective forms of psychological support. Team members need to maintain a consistently positive approach both to patients and to their progress at rehabilitation; there is much anecdotal evidence for the way in which a careless negative remark can profoundly demoralize a patient. Demonstrating respect for a patient as an individual fosters feelings of self-worth and enhances motivation. However,

attempts to providing positive feedback should never lead to dishonesty or insincerity and care must be taken not to generate false expectations.

The need for the psychological support of spouses, partners and other relatives should not be forgotten. In hospital-based rehabilitation settings, patients can offer one other support and encouragement – the so-called 'therapeutic community'. Self-help groups are particularly useful in providing ongoing psychological and practical support following discharged from the rehabilitation programme.

Discharge planning and follow-up

Discharge from hospital should signal a transition in the rehabilitation process rather than its conclusion. Many patients benefit from continuing outpatient therapy aimed at achieving further gains or preventing the loss of what has been achieved. Follow-up arrangements will depend on the needs of the individual and the availability of services. Some follow-up is essential so that any exacerbation of activity or participation restriction can be evaluated and, if possible, remedied.

Evaluation

Rehabilitation programmes are resource intensive and must therefore demonstrate their effectiveness. At a minimum, data should be collected to allow comparison of people on entry and at discharge. Data collection is becoming increasingly standardized; this facilitates comparison between facilities and between different treatment strategies. Such research is now coming of age and holds promise that we will not only be able to prove the overall efficacy of rehabilitation programmes, but also to identify the key elements that contribute to success.[30]

The rehabilitation setting

Rehabilitation can be provided in various settings, including stand-alone rehabilitation hospitals, designated rehabilitation units in general hospitals, undifferentiated hospital wards, nursing homes and residential care centres, day hospitals, community day centres, outpatient rehabilitation centres, and the patient's own home. Each of these has specific advantages and disadvantages, detailed discussion of which is outside the scope of this chapter. Ideally, a range of options should be available to meet the needs of individual patients at a given time.

In larger hospitals, it is usual to co-locate patients with similar rehabilitation needs. Thus, for example, stroke units and ortho-geriatric units have long been in fashion. Such units foster staff expertise and facilitate research, education and training. Though stroke units have been shown to improve survival and functional outcomes,[36] evidence for the efficacy of ortho-geriatric units is less convincing.[37]

Community-based rehabilitation has recently come of age as a compliment to hospital-based rehabilitation. In practice, it only suits patients from the least disabled end of the spectrum and who are otherwise well supported in the community. 'Intermediate care' is a term to describe intensive, short-term, community or home-based rehabilitation that aims to prevent hospitalization, to facilitate early discharge from hospital and/or to maximize independent living.[38]

Emerging technologies and rehabilitation

New technologies have enormous potential in both the assessment and management of the older person in the rehabilitation setting. Many of the existing scoring systems used to quantify disability and document progress (see Table 114.3) are subjective and prone to inter- and intra-observer variability or bias. They are also time-consuming and divert therapists from providing more direct patient care. Remote measuring devices or sensors can objectively record quantitative data and measure an individual's progress in rehabilitation. They can indicate when full rehabilitation potential has been reached or demonstrate ongoing improvement and the need for ongoing therapy.

Technology also has research potential and can provide more accurate evidence of efficacy of interventions (including pharmacological intervention) in clinical trials. For example, a simple accelerometer might be better than a traditional scoring system[39] in demonstrating subtle but important gains in mobility with new drug treatment in a patient with Parkinson's disease.

Technology can also help to tailor a rehabilitation programme to the unique requirements of the individual patient. For example, it can be used to accurately assess a maladaptive gait pattern in a person with osteoarthritis and thus indicate the most appropriate orthotic device to prescribe.[40]

The development of advanced robotic devices to assist in rehabilitation programmes in select patients is equally becoming a reality. The Honda Motor Company is researching a walking assist device which has the potential to not only augment recovery in patients with neuromuscular deficits, but to provide ongoing assistance with activities of daily living including stair walking (Figure 114.2).

Development of devices

Until recently, the clinical use of remote sensor devices was limited by their bulk, weight and battery life. They were often difficulty to attach and there were problems with data storage and transmission. Recent advances in miniaturization, ergonomic design and the availability of wireless transmission have generated patient-friendly devices that

Figure 114.2 Honda's experimental Walking Assist Device with Body Weight Support System. Reproduced by permission of Honda Motor Co., Ltd.

can transmit massive amounts of data for analysis. While devices including accelerometers are now widely used in the gaming industry, their scientific validation in the rehabilitation of older patients is limited.

'Virtual reality' (VR) platforms can provide safe and novel treatment for the older patient with rehabilitation needs. They can provide visual, auditory and tactile sensory input and when used in conjunction with robotic devices, they can also assist with motor skills. For example, a 'robotic glove', when combined with a virtual reality platform can optimize motor function following a hemiparetic stroke. The device can then be attached to an arm orthosis which can be adjusted to overcome gravity by passively counterbalancing arm weight, and providing sensory feedback through virtual environments.[41]

'Video capture' technology combined with remote sensor technology provides an added dimension. Specifically, head-mounted devices designed to track head movements have been used to enhance the virtual environments of patients recovering from stroke.

There have been attempts to use VR platforms to counter impaired postural control and thus reduce falls and injury.[42] In maintaining balance, we know that the CNS integrates visual, vestibular, proprioceptive and somatosensory stimuli. As the intensity and integration of these stimuli decline with advancing age, adaptive mechanisms cause older adults to rely more on visual stimuli and to initiate fewer head movements.[43] By altering sensory inputs and enhancing appropriate corrective strategies, VR can augment such adaptive mechanisms, thus promoting postural stability. VR also provides a safe virtual environment where rehabilitation activities can be risk free and promote patient confidence.

Current barriers to the wider use of sensory-based technological systems include their cost, lack of technical support and a strong evidence base for their efficacy. 'Video capture' technology is, however, much cheaper and is widely available. The gaming industry has been instrumental in developing such systems as the Nintendo Wii, with its built-in accelerometers and infrared camera to track movement. Thus, the potential to develop game-like activities to support rehabilitation already exists. Features designed to enhance motivation, to improve motor function, to reach and to grasp can all be incorporated into specific games. Video games that focus on upper limb function following stroke are being developed. Such games should be meaningful (i.e. provide feedback), should avoid conveying a sense of failure and should try to match the level of challenge to the capability of the player.[41]

Rehabilitation at home

Remote sensors, wireless data transfer (perhaps in combination with global positioning systems – GPS – technology) robotics and mobile computer systems also facilitate early transfer from hospital-based to home-based rehabilitation programmes. Cost savings, reduced hospital-acquired infections and return to familiar environments are just some of the advantages. Such technology can then continue to be used to maintain independence, reduce caregiver burden and prevent institutionalization.

Specific rehabilitation problems

Cardiac rehabilitation

Cardiac rehabilitation is defined as:

> The process by which patients with cardiac disease, in partnership with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychological health.[44]

It has evolved over the past 60 years, since early mobilization following myocardial infarction was first recommended.[45] Initial programmes were exercise-based and successfully reduced post-infarct morbidity and mortality, with a 27% reduction in all cause mortality being reported.[46] More recently, it has been shown that three months of exercise training in older patients following acute myocardial infarction, improves exercise capacity and a range of biochemical and physiological markers of cardiac performance.[47]

The scope of cardiac rehabilitation has now expanded to include other conditions (e.g. ischaemic heart disease, cardiac failure, coronary revascularization, valve replacement surgery). Modern interventions include education, psychological support, lifestyle advice, risk factor reduction and drug therapy.[48] Home-based programmes complement those that are hospital-based and these particularly suit some elderly people. Outcomes increasingly focus on improved exercise tolerance and quality of life in addition to reduced mortality.[49]

Guidelines on cardiac rehabilitation devised by the Scottish Intercollegiate Guidelines Network (SIGN) have been endorsed by the British Association for Cardiac Rehabilitation and identify four phases of rehabilitation as outlined in Table 114.4.

In Phase 1, early mobilization reduces the risk of thromboembolic disease and other complications of immobility. Low-level self-care activities can begin shortly after the acute event and then gradually increase. Thus, people with an uncomplicated infarct might feed themselves from the outset, sit out of bed within 24 hours and walk to the toilet within 48 hours. Spouses, partners and other family members are ideally involved from this initial stage and should also be offered reassurance and information.

The early post-discharge period (Phase 2) is often a time when patients and families are apprehensive and need support. This can be provided by written information and a telephone 'help line'. Though Phase 3 revolves around a structured and tailored exercise programme, this is just one of its elements (Table 114.4). This phase is increasingly offered in the community rather than in hospital. Physical activity and lifestyle changes need to be maintained (Phase 4) if the gains of rehabilitation are to be sustained. Many people benefit from involvement in a local cardiac support group and participation in group activities.

A detailed description of the exercise programmes suitable for people with cardiac disease is available elsewhere.[44] An initial assessment is essential to identify high-risk patients who either need a modified exercise programme and/or who need to be carefully monitored. Ideally, this will include a simple test of functional capacity such as a shuttle walking test [50] or a six-minute walking test.[51] High-risk patients need careful evaluation, perhaps including an exercise stress test.

Table 114.4 The four phases of cardiac rehabilitation.

1 The inpatient stage, following an acute cardiac event includes medical evaluation, reassurance, education and correction of misconceptions, risk factor assessment, mobilization and discharge planning.
2 Following hospital discharge, when patients may need physical and psychological support.
3 Structured exercise training, together with continuing educational and psychological support and advice on risk factor reduction.
4 Long-term maintenance of physical activity and lifestyle change.

Aerobic, low to moderate intensity exercise is appropriate for the majority of elderly patients in a cardiac rehabilitation programme. This is generally undertaken in a group setting and at least twice weekly for a minimum of eight weeks. However, weekly hospital-based group exercise, together with a home-based exercise programme can be just as effective.

The intensity of exercise can be monitored by perceived exertion or by heart rate, as measured with a pulse monitor. With the former, the aim is to achieve 'comfortable breathlessness'. The target heart rate is derived from the maximal heart rate (estimated at 220-age in years). A training effect is best seen at 65–80% of maximal heart rate.[52]

Patients with unstable angina, valve stenosis or cardiac failure, or with a history of cardiac arrhythmia, are most at risk of an exercise-induced cardiac event. Such patients require a particularly careful evaluation before starting rehabilitation and close medical supervision thereafter. Warm-up and cool-down exercises minimize the risk of musculoskeletal injury and cardiac arrhythmia. Extremes of temperature and over-exertion should be avoided and exercise should cease immediately if the person feels unwell. All symptoms should be reported and medically assessed.

Access to a formal cardiac rehabilitation programme is not always possible and is inappropriate for elderly people with coincidental respiratory, neurological or musculoskeletal disorders. However, even chair-bound elderly people benefit from low-intensity exercise following a cardiac event.

As psychosocial factors predispose to heart disease,[53] it is not surprising that they are particularly prevalent following an acute cardiac event. Thus, over 40% of elderly patients have some depressive symptoms following acute myocardial infarction.[12] Psychological distress in the early post-infarction period predicts a subsequently reduced QOL.[54,55] Though psychological rehabilitation aims to reduce distress, evidence of its efficacy is conflicting.[56,57] The key components are relaxation, stress management and counselling for individuals or groups.

Patient education is the final element of cardiac rehabilitation and should span the entire programme. Activities can range from the highly structured and formal to the informal and opportunistic. Patients need to understand their disease, its implications and the prospect of recovery. They also need to know about underlying risk factors and the scope for secondary prevention. Lifestyle modification should be recommended for those who smoke, are obese, hypertensive, or with lipid abnormalities. Ideally, spouses, partners and other family members should be involved in educational activities.

Pulmonary rehabilitation

Pulmonary rehabilitation is defined as:

> An art of medical practice wherein an individually tailored, multidisciplinary programme is formulated which through accurate diagnosis, therapy, emotional support and education, stabilizes or reverses both the physio- and psycho-pathology of pulmonary disease and attempts to return the patient to the highest possible functional capacity allowed by his pulmonary handicap and overall life situation.[58]

For people with chronic obstructive pulmonary disease (COPD), pulmonary rehabilitation reduces dyspnoea and fatigue, enhances patient control of the disease and increases exercise capacity.[59] It also improves QOL[58] and may prevent hospitalizations.[60] Similar levels of benefit are seen in all adults, including the 'old old'.[61,62] Indeed, the greatest benefits from pulmonary rehabilitation are found in the most impaired patients.[63] People with other significant chronic lung diseases (e.g. asthma, interstitial/restrictive lung disease) also benefit from rehabilitation.[64]

The key elements of pulmonary rehabilitation are summarized in Table 114.5. An initial assessment allows the programme to be tailored to the individual. While clinical and laboratory tests (e.g. radiology, pulmonary function tests) help to define the nature and severity of lung disease, these are unlikely to improve with rehabilitation. Formal exercise testing, together with blood gas analysis (or oximetry) and cardiac monitoring, should be performed at this stage to determine exercise tolerance, the tendency to hypoxia and the risk of cardiac dysrhythmia. For those who are hypoxic at rest or who desaturate with exertion, a modified exercise programme with supplementary oxygen and appropriate monitoring might still be feasible.[65]

Table 114.5 Elements of pulmonary rehabilitation.

Assessment
Define the nature and severity of lung disease
Identify continuing risk factors
Identify comorbidities
Assess nutritional status
Check immunization status (especially against *Pneumococcus* and influenza)
Assess lifestyle factors contributing to activity and participation restriction
Exercise test ± blood gas analysis/oximetry ± ECG monitoring
Intervention
Optimize medical management
Exercise programme
Breathing exercises
Patient education
Lifestyle and dietary modification
Psychosocial support
Follow-up
Establish benefits of rehabilitation
Assess need for continued rehabilitation

Exercise training is the cornerstone of the rehabilitation process and both upper and lower limb exercises improve limb strength and exercise tolerance.[58] Ventilatory muscle training only benefits a minority of patients with COPD. Ideally, exercise should be undertaken three times weekly, should last a minimum of 20 minutes, should induce a heart rate of not less than two-thirds of the maximum expected in the absence of lung disease, and should last at least 6 weeks and preferably 3 months.[66]

In most centres, group exercise programmes are conducted in outpatient settings. Based on the initial assessment, a programme of graded exercises is provided for each individual, leading to a gradual increase in exercise capacity and tolerance. Exercise protocols for people with mild, moderate and severe chest disease are available.[67]

Education aims to enable patients to develop a greater understanding of their disease and the factors contributing to its progression and retardation.[67] Lifestyle and dietary modifications may be required and people may need practical help to achieve these. For example, those who smoke not only need to understand the consequences and the advisability of stopping, but may also need access to smoking cessation programmes. Psychosocial support involves techniques to reduce anxiety and depression; however, there is no clear evidence of their efficacy.[57]

The gains achieved through pulmonary rehabilitation are often lost over time without specific strategies to maintain them.[68] While some form of follow-up is always required, a continuous maintenance programme is ideal. In this regard, self-help groups who encourage and support one another are particularly valuable.

Musculoskeletal disorders

This is a collective term for many heterogeneous conditions that differ in their duration (i.e. acute, sub-acute or chronic), aetiology (e.g. traumatic, inflammatory, degenerative) and the tissues involved (e.g. bone, joint, muscle). They are the commonest cause of disability in old people, such that in the United States, almost 60% of people aged 65 years and over report arthritis or chronic joint symptoms.[69] Such problems will affect over 41 million older Americans by 2030.[70]

Despite their heterogeneity, musculoskeletal disorders tend to result in similar restrictions in activity and participation. Pain, reduced mobility and other functional losses are prominent and these are inter-linked and tend to reinforce one another. For example, people with arthritis may avoid those activities that exacerbate joint pain. As a

result, muscles are weakened and joints become unstable and easily injured. This leads to more pain and further avoidance of exercise. Cardio-respiratory fitness may then become critically reduced, particularly in the very old in whom activities of daily living require oxygen uptakes close to the age-associated maximum. The net result is an unfit, inactive, arthritic person whose independence is compromised.

Detailed discussion of the non-pharmacological and pharmacological management of musculoskeletal pain is dealt with elsewhere in this text (see Section 9). However, it should be emphasized that accurate diagnosis is a prerequisite for rational drug prescribing. If analgesics are required, the timing of their use is important. For example, as pain in osteoarthritis is often exacerbated by exercise, it is best to medicate beforehand. Non-pharmacological approaches to pain management should also be considered. For example, moulded splints can protect arthritic hand joints and allow pain-free function with minimal loss of dexterity. A cane held in the contralateral hand limits pain by reducing weight on an arthritic hip. For knee pain, the patient should experiment with holding a cane in either hand. Cane length is important to avoid secondary problems with other joints. Length should equal the distance from the wrist crease to the floor. Stick rubbers should be regularly checked and replaced when worn, to reduce the risk of falls. Resistant pain is best managed by a multidisciplinary approach and nowadays most large centres have access to a pain management team and with it the expertise of anaesthetists, psychiatrists and others.

Daily range-of-motion exercises are particularly important in attempting to restore function in arthritic joints. However, compliance with such measures is low for people of all ages. Joining others in group activities adds a social component and increases compliance. Footwear must be appropriate. Patients with painful knees will benefit from wearing soft-soled shoes with cushioned heels (e.g. jogging shoes). A rocker bottom shoe (Figure 114.3) can reduce pain from rigid toes by assisting in weight transfer from posterior to anterior. This reduces the force needed to propel the body over the metatarsophalangeal (MTP) joints. Metatarsalgia can be reduced by an internal pad placed proximal to the MTP joints. When the hind foot is involved through medial arch collapse, an orthosis which supports the medial arch often helps. Heat, including baths and spas, has been traditionally used for arthritic joints. There is no evidence that hydrotherapy causes measurable functional improvement in arthritic joints, although it does promote self-confidence.[71]

With regard to loss of function, a home-based assessment by an OT is often invaluable. Simple ergonomic measures and aids (e.g. tap turners, zipper pulls, sock pulls, stretch laces, long-handled shoe-horns and Velcro fasteners) can notably reduce joint strain and consequent pain.

Figure 114.3 Rockerbottom shoe with an insole.

Pathological changes occur against a backdrop of age-related changes in joints and soft tissues, which themselves limit flexibility. However, these age-related changes are reversible and exercise will increase joint flexibility[72] and improve the strength, size and resilience of cartilage, ligaments and muscles. The arthritic patient should be encouraged to develop physical fitness and set realistic goals.

In the context of musculoskeletal disorders, there is little evidence for the efficacy of structured rehabilitation programmes perhaps because research of sufficient rigor has yet to be undertaken. Multidisciplinary rehabilitation, based on time-limited and goal-directed interventions, is only of proven benefit in the management of chronic back pain, other types of chronic pain and following hip fracture in frail elderly people.[73] The prevalence and impact of musculoskeletal disorders on elderly people, means that further research to identify the effective elements of rehabilitation should become an even greater priority.

The elderly amputee patient

Most lower limb amputations in elderly patients are a consequence of peripheral vascular disease.[74] While limb-threatening ischaemia is occasionally due to a sudden embolic event, most patients have a long period of worsening ischaemia prior to amputation. Many people are diabetic and have coexisting cardiac and other vascular disease, while others have smoking-induced chronic lung disease. Despite this, rehabilitation has much to offer the older amputee[75] and many rise to the challenge of walking even with bilateral below-knee prostheses.

That stated, elderly people who require a lower limb amputation are a high-risk group. Perioperative mortality

is in the range of 10–30%, two-year survival is 40–50% and five-year survival is 30–40%. These rates have not changed significantly in the past 50 years, even with better anaesthetic and surgical techniques.[76]

When faced with an ischaemic limb that cannot be salvaged by vascular reconstruction, the surgeon often has to choose between a transfemoral (i.e. above-knee) or transtibial (i.e. below-knee) amputation. Preservation of the knee is critical in maintaining proprioceptive and neuromuscular control and particularly in minimizing energy expenditure. It takes 40% more energy to walk with an above-knee than with a below-knee prosthesis.[77] However, injudicious efforts to salvage a knee joint can result in an ischaemic stump which fails to heal and later necessitates a more proximal amputation. The need for a second surgical procedure is potentially disastrous as it increases the anaesthetic risk, prolongs the period of immobility, increases the risk of deconditioning and delays entry into rehabilitation.

Following limb amputation, stump management involves the use of rigid removable dressings to reduce oedema, promote healing and protect against incidental trauma. It is important that early physical therapy be directed at strengthening the arms, the abdominal muscles, the lower back and the remaining leg. Irrespective of age, prescription of a lower limb prosthesis is almost always indicated, even in the presence of other major medical problems. However, it has been shown that older amputees are less likely than their younger counterparts to receive a prosthesis, even when potential confounding factors such as comorbidities and functional status are considered.[78]

The prosthesis facilitates transfers, standing and walking and has cosmetic value. It used to be argued that an older amputee should have crutch-walking capacity before being offered a prosthesis. However, as walking without bearing weight on the amputated side has a higher energy cost than walking on the prosthesis, this criterion is invalid. While some refuse a prosthesis and accept wheelchair mobility, most elderly people and particularly those with few comorbidities, are happy with their prosthesis and use it well.[79] As with any other medical intervention, a prosthesis should never be prescribed without considering the unique needs and wishes of each patient. The demands of using a prosthesis should be fully explained. For a below-knee amputee, the full range of knee extension should be maintained. It is therefore important to avoid prolonged periods of sitting without corrective exercises and a minimum of 20–30 minutes of prone lying should occur twice daily to promote full extension. The skin coming into contact with the prosthesis needs to be durable and toughened; this is best achieved by graded use of the prosthesis. Massaging the stump improves circulation and prevents adhesions during the healing process and patients should be encouraged to do this.

Figure 114.4 Two types of lower limb prostheses are shown with a solid ankle-cushion heel (SACH) foot on the left and an articulated flexible ankle mechanism fitted on the right prosthesis, which additionally shows the central pylon before final covering.

Modern trans-tibial prostheses consist of a socket, a shank and an ankle and foot mechanism (Figure 114.4). The socket is the major determinant of the comfort and stability of the prosthesis. In general, it is designed to transfer most of the weight onto the patellar tendon and a good fit is critical. The stump will be oedematous in the early post-operative period and then shrinks over time. Temporary sockets are therefore required until this process is complete and a permanent socket is cast. Plastic laminate is the most commonly used socket material. The socket may incorporate a suction device to suspend the limb. When a non-suction socket is used, an interface material (stump socks or other plastic resilient material) is needed. Stump socks should be washed daily with mild soap and warm water, rinsed thoroughly and allowed to dry flat. The inner surface of the socket should be cleaned each evening with a warm soapy cloth.

Shanks have traditionally had an 'exoskeletal' design, using willow or lightweight balsa wood covered with laminated plastic. A more modern 'endoskeletal' limb (Figure 114.4) has a central pillar, made of carbon-fibre

or lightweight metal to support the body weight, and is surrounded by a soft cover approximating the feel of a normal limb.

A prosthetic foot may be rigid or have an ankle that allows movement in one or more planes. Prescription is dependent on the level of client activity and on the condition of the stump. There is no evidence that any one design is inherently superior.[80] The advantages of a rigid ankle are lightness, low initial and maintenance cost, easy fitting and good appearance. The solid ankle-cushion heel (SACH) foot has a rigid ankle, a compressible heel and a light foot. It is particularly suited to the frail, less active patient who does not take long steps. SACH feet provide long service and are now almost always used for below-knee limbs.

Once a comfortable, stable and functional limb has been provided, the next stage of training is to help the patient to walk on it properly. Gait retraining and the provision of additional mobility aids are complex subjects, discussion of which is outside the scope of this chapter.

When peripheral vascular disease leads to limb amputation, the remaining limb is often significantly ischaemic such that 15–20% of people undergo a contralateral amputation within two years and some 40% within four years.[81] The viability of the remaining leg can often be enhanced by surgery and by minimizing risk factors for vascular disease (e.g. poor diabetic control, cigarette smoking, etc.). Foot hygiene should be promoted and trauma to the leg should be avoided, particularly by wearing appropriate footwear.

Comprehensive rehabilitation of the elderly amputee involves more than the provision of a prosthesis. Comorbidity, prosthetic component selection and resettlement with tenuous or absent social supports all present formidable challenges. A more comprehensive review of this area, including the care of the bilateral amputee, is available.[82]

The non-painful sensation of a phantom limb is normal after amputation. Initially, this can be so deceptive that a patient inadvertently attempts to walk or to scratch the missing limb. Over time, patients sense the limb retracting or 'telescoping' into the stump. Phantom pain is a separate though perhaps related phenomenon, which affects some 50–80% of people following a limb amputation.[83]

The pathophysiology of phantom pain is poorly understood, though central and peripheral nervous system factors together with psychological factors are implicated.[79] It can usually be differentiated from stump pain, as it is localized in the phantom and is variously described as burning, crushing or lancinating. Phantom pains may be continuous or intermittent and the limb may be perceived as twisted or deformed. Management includes explaining the nature of the phenomenon to the patient. While patients with chronic pain before amputation have a higher incidence of phantom pain, attempts to control pain before and during surgery do not consistently reduce the subsequent development of phantom pain.

The management of phantom pain is challenging, particularly on the rare occasion when it is very debilitating. There is little evidence from randomized controlled trials to guide clinicians and when reported, improvement rates are little better than with placebo.[84] Anaesthetic and surgical techniques (e.g. local anaesthesia, sympathectomy, cordotomy) are as disappointing as pharmacological approaches. Tricyclic antidepressants and sodium-channel blocks are often used because of their efficacy in neuropathic pain, but are of no proven benefit. Transcutaneous electrical nerve stimulation (TENS) provides modest relief at best[85] and patients need ongoing psychological help to develop coping strategies.[86]

Neurological rehabilitation

The pathological processes that involve the brain and other parts of the nervous system tend to divide into those that are acute and non-progressive (e.g. stroke, acquired brain injury, spinal cord injury) and those that are chronic and progressive (e.g. Parkinson's disease, motor neurone disease). Collectively, they present an array of rehabilitation challenges, particularly relating to mobility, balance and stability, communication and swallowing, and cognition. The management of chronic pain in older people can be a particular challenge.[87]

This brief section deals only with the rehabilitation of some common chronic progressive neurological disorders of old age. The complex area of rehabilitation following stroke is addressed elsewhere in this text (Chapter 58), while acquired brain injury and spinal cord injury are so uncommon in elderly people as to not warrant discussion here.

A key matter to consider is the rationale for rehabilitation in people with progressive neurological disorders as it can be argued that their relentless nature makes resource-intensive approaches to rehabilitation inappropriate. This raises complex ethical and practical issues regarding the overlap between rehabilitation and palliative care. In the context of a progressive dementing illness, particular challenges arise when, for example, patients lack both the intellectual capacity to fully engage in rehabilitation and to provide informed consent to participate. However, the loss of intellectual capacity cannot justify a decision to deny a person access to potentially beneficial therapy.

With progressive neurological disorders such as Parkinson's disease, rehabilitation has tended to focus on gait and speech problems.[88] While these are often the most distressing aspects of the disease, they are also the most difficult to modify with remedial therapy.[89,90]

Dementia is by far the commonest progressive neurological disorder in older people. Here, two particular considerations arise: the impact of rehabilitation on the dementing process *per se* and the impact of a coincidental

dementia on rehabilitation for another disorder (e.g. hip fracture or stroke). With regard to the former, most research to date has focused on the potential benefits of exercise; a meta-analysis of 30 trials involving over 2000 patients concluded that exercise training increases fitness, physical function, cognitive function and positive behaviour in people with dementia.[91] There is also evidence that those with mild to moderate dementia benefit from rehabilitation for such problems as hip fracture.[92]

Future challenges

While the principles and practice of rehabilitation have evolved considerably in recent decades, progress has been slow in at least two areas. The first concerns access to rehabilitation for elderly people even in countries with well-developed health services. For example, it is estimated that only 2% of Canadians who might benefit access pulmonary rehabilitation and only 1% of those in need access musculoskeletal rehabilitation.[93,94] The mis-match between resources and demand is even greater in developing countries.

The second area of slow progress is in identifying the most cost-effective elements of rehabilitation in different clinical situations. Further research in this area is essential for resources to be optimally targeted, for funding to be secured and for geriatric rehabilitation to advance as a discipline. Many healthcare systems are struggling with demographic change and a consequent increased demand for hospital resources at a time when acute hospital beds are being reduced. As acute hospital care and long-term residential care tend to be separately funded and poorly coordinated, pressures to reduce lengths of acute hospital stay tend to erode rehabilitation services in the acute hospital. Community-based rehabilitation services are not expanding to fill the gap and are anyway unsuited to many elderly people who lack the live-in support of a carer.

A lack of investment in rehabilitation is a false economy as it leads to avoidable and costly institutional care.[95] Sixty years ago, Marjorie Warren highlighted the social injustice of failing to optimally meet the rehabilitation needs of elderly people and their families. Such concerns are still relevant today.

Key points

- In 2001, the WHO introduced its International Classification of Functioning, Disability and Health (ICF). This challenges traditional views on health and disability, while providing a mechanism to document the impact of the social and physical environment on a person's functioning.
- Rehabilitation is a step-wise process where the various stages often overlap, may occur concurrently and may need to be regularly revisited.
- Education is a vital component of rehabilitation as through it the patient acquires the knowledge, skills and attitudes to minimize the activity and participation restrictions that can result from impairment.
- A failure to optimally meet the rehabilitation needs of older people and their families is socially unjust, just as a lack of investment in rehabilitation is a false economy, leading to avoidable and costly institutional care.

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SECTION 14

Iatrogenic Infections

CHAPTER 115

Tuberculosis

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Introduction

In 2008, the World Health Organization (WHO) estimated 8.9–9.9 million incident cases of tuberculosis (TB), 9.6–13.3 million prevalent cases of TB, 1.1–1.7 million deaths from TB among HIV-negative people and an additional 0.45–0.62 million TB deaths among HIV-positive people.[1]

In the USA, during the past three decades, the excess in morbidity reflected a changing epidemiological pattern. HIV infection, poverty, homelessness, substance abuse and immigration from countries with a high prevalence of TB have all contributed to TB morbidity. Overburdened public health TB services were not only unable to manage the resurgence in the 1980s but were also unprepared to cope with emerging multidrug resistance. From the mid-1990s to the present, aggressive TB control, implementation and enhanced resources have resulted in a substantial decline in the overall incidence of TB.

The geriatric population across all racial and ethnic groups and both genders is at substantial risk for *Mycobacterium tuberculosis* (*Mtb*) infection, perhaps because of both biological (compromised nutrition and immune status, underlying disease, medications and possible racial predisposition) and socioeconomic factors (poverty, living conditions and access to healthcare). Frail elderly residents of nursing homes and other long-term care facilities are the most vulnerable group. Because of the highly communicable potential of *Mtb*, the inevitable endemic transmission between residents and from resident to staff has been demonstrated in such facilities. (For the purpose of clarity, TB infection, or latent TB, refers to contained and asymptomatic primary infection with a positive tuberculin skin test reaction, whereas TB disease indicates overt clinical manifestations of TB.)

The Institute of Medicine report *Ending Neglect: the Elimination of TB in the United States*, which was undertaken through sponsorship from the Centers for Disease Control and Prevention (CDC) in 2000, reviews the lessons learned from the neglect of TB between the late 1960s and the early 1990s and reaffirms commitment to a more realistic goal of elimination of TB in the USA.[2] The WHO report *Global Tuberculosis Control: a Short Update to the 2009 Report* includes the latest (2008) estimates of the global burden of TB (incidence, prevalence and mortality).[1] It also includes an assessment of progress in implementing the Stop TB Strategy and the Global Plan to Stop TB to achieve the 2015 global targets for TB control. These targets are that incidence should be falling by 2015 (Millennium Development Goal Target 6.c) and that prevalence and mortality rates should be halved by 2015 compared with their level in 1990.

This chapter reviews the current global epidemiology, pathogenesis, clinical characteristics, diagnosis, management and prevention of *Mtb* infection in community-dwelling and institutionalized ageing adults.

Epidemiology

More than 2 billion people (about one-third of the world population) are estimated to be infected with tuberculosis.[1] The global incidence of TB peaked around 2003 and now appears to be declining slowly. In 2006, the WHO estimated the prevalence of active infection to be 14.4 million and the incidence of new cases 9.2 million; 12 of the 15 countries with the highest estimated TB incidence were reported to be in Africa.

Developed nations including the USA and parts of Southeast Asia report an estimated 380 million persons infected with *Mtb*; about 80% of infected persons in Europe are 50 years of age or older.[3]

In the USA, TB prevails among the foreign-born and minorities. From 1985 to 1992, TB incidence increased among all ethnic groups except non-Hispanic whites and Native Americans/Alaskan Natives. From 1992 to the present, the overall incidence of TB in the USA declined by

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over 45%, largely because of improved funding resources channelled into TB control programmes, which allowed for the implementation of directly observed therapy (DOT). However, the percentage of cases among foreign-born persons increased disproportionately from 27% in 1992 to 46% in 2000.[4] In 2009, the CDC reported 11 540 TB cases; the TB rate was 3.8 cases per 100 000 population, a decrease of 11.4% from the rate of 4.2 per 100 000 reported for 2008.[5] The 2009 rate demonstrated the greatest single-year decrease ever recorded and was the lowest recorded rate since national TB surveillance began in 1953. TB case counts and rates decreased substantially among both foreign-born and US-born persons, although foreign-born persons and racial/ethnic minorities continued to have TB disease disproportionate to their respective populations, and nearly 11 times higher than in US-born persons. The rates among Hispanics and blacks were approximately eight times higher than among non-Hispanic whites and rates among Asians were nearly 26 times higher. The large decrease in reported cases during 2009 might represent a decrease in TB disease resulting from changes in population demographics or improved TB control.

TB also occurs with disproportionate frequency among the elderly.[6,7] Elders living in communal settings such as nursing homes or other long-term care facilities have a TB incidence rate approximately four times greater than the general population.[8] The aggregate TB incidence rate for nursing home residents is 1.8 times higher than the rate seen in community-dwelling elderly.[9] The enhanced efficiency of TB transmissibility within congregate settings such as prisons, nursing facilities (nursing homes), chronic disease facilities and homeless shelters has raised concerns about TB infection and disease in the institutionalized elderly.[10,11] Positive tuberculin reactivity associated with prolonged stay among residents of long-term care facilities for the elderly has been demonstrated, implying an increasing risk of TB infection.

Pathogenesis

The pathogenesis of TB infection and disease begins in most cases with the inhalation of the tubercle bacilli.[12] The usual inoculum is no more than 1–3 organisms, which are taken up by alveolar macrophages and carried to regional lymph nodes. Spread may occur via the lymphohaematogenous route with dissemination to multiple organs. From 2 to 8 weeks after infection, cell-mediated immunity (CMI) and delayed-type hypersensitivity (DTH) responses develop, leading to the characteristic reactive tuberculin test and to the containment of infection. Chemoattractants cause monocytes to enter the area and become transformed into histiocytes forming granulomas. Although the bacilli may persist within macrophages, additional multiplication and spread is curtailed. Healing usually follows with calcification of the infected focus. Caseous necrosis may result secondary to the immune response. Erosion into a bronchiole causes cavity formation where bacilli can multiply and spread. Solid necrosis can result from production of hydrolases from inflammatory cells causing tissue liquefaction and creating a prime medium for microbial replication, generating up to 10 billion bacilli per millilitre. Individuals who develop active disease either fail to contain the primary infection or develop reactivation as a result of relative or absolute immune suppression at a point remote from primary infection. This is most likely to occur in immunocompetent adults within the first 3 years after exposure. Factors related to progression of disease reflect a weakened immune status and include physiological states, for example, normal ageing; associated intercurrent disease – particularly diabetes mellitus, malignancies causing primary immunosuppression or requiring toxic chemotherapy or corticosteroid-dependent diseases such as asthma or collagen vascular disease; poor nutritional status particularly related to alcohol and drug abuse; smoking and HIV infection. Although it is likely that the increased frequency of TB in the elderly could partly be due to CMI that is impaired by senescence (shown in murine models), other concomitant age-related diseases (diabetes mellitus, malignancy), chronic kidney disease and renal insufficiency, poor nutrition and immunosuppressive drugs may also contribute to this increase.[13] In the elderly, approximately 90% of TB disease cases are due to reactivation of primary infection. Persistent infection without disease may occur in 30–50% of individuals. Some elderly persons previously infected with *Mtb* may eventually eliminate the viable tubercle bacilli and revert to a negative tuberculin reactor state. These individuals are therefore at risk of new infection (reinfection) with *Mtb*. There are therefore three subgroups of older persons potentially at risk for TB: one subgroup never exposed to TB that may develop primary TB disease, a second subgroup with persistent and latent primary infection that may reactivate and a third subgroup that is no longer infected and consequently at risk for reinfection.

Clinical characteristics

Clinicians must be aware that frail older persons with TB disease may not demonstrate the overt and characteristic clinical features of TB such as fever, night sweats or haemoptysis. They may exhibit atypical and subtle clinical manifestations of 'failure to thrive' with loss of appetite, functional decline and low-grade fever or weight loss.[13] Although several published works have attempted to delineate clear differences between younger and older TB patients, such studies have provided variable findings. In a meta-analysis of published studies, comparing pulmonary TB in older and younger patients, evaluating

the differences in the clinical, radiological and laboratory features of pulmonary TB, no differences were found in the prevalence of cough, sputum production, weight loss, fatigue/malaise, radiographic upper lobe lesions, positive acid-fast bacilli (AFB) in sputum, anaemia or haemoglobin level and serum aminotransferases.[14] A lower prevalence of fever, sweating, haemoptysis, cavitary disease and positive purified protein derivative (PPD), and also lower levels of serum albumin and blood leukocytes, were noticed among older patients. In addition, the older population had a greater prevalence of dyspnoea and some underlying comorbid conditions, such as cardiovascular disorders, chronic obstructive pulmonary disease, diabetes mellitus, gastrectomy history and malignancies. This meta-analytical review identified some subtle differences in clinical presentations of older TB patients compared with their younger TB counterparts. However, most of these differences can be explained by the already known physiological changes that occur during ageing. The majority of older TB patients (75%) with *Mtb* disease manifest active disease in their lungs.[14] Extrapulmonary TB in the elderly is similar to that in younger persons and may involve the meninges, bone and joint and genitourinary systems or disseminate in a miliary pattern.[15–19] Infection of lymph nodes, pleura, pericardium, peritoneum, gall bladder, small and large bowel, the middle ear and carpal tunnel have been described in the literature. Because TB can involve virtually any organ in the body, this infection must be kept in the differential diagnosis of unusual presentations of diseases, especially in the elderly. Thus, TB has been aptly described as 'the great masquerader' of many diseases.

Diagnosis

Clinicians caring for the elderly must maintain a high index of suspicion for TB when possible, in order to recognize and treat infected individuals promptly.

Tuberculin skin testing

The Mantoux method of tuberculin skin testing using the Tween-stabilized purified protein derivative (PPD) antigen is one of the diagnostic modalities readily available to screen for TB infection, despite its potential for false-negative results.[20] In the elderly, because of the increase in anergy to cutaneous antigens, the two-step tuberculin test is suggested as part of the initial geriatric assessment to avoid overlooking potentially false-negative reaction.[21] The American Geriatrics Society routinely recommends two-step tuberculin testing as part of the baseline information for all institutionalized elderly.[22] The two-step tuberculin skin test involves initial intradermal placement of five tuberculin units of PPD and the results are read at 48–72 h. Patients are retested within 2 weeks after a negative response (induration of less than 10 mm). A positive 'booster effect', and therefore a positive tuberculin skin test reaction, is a skin test of 10 mm or more and an increase of 6 mm or more over the first skin test reaction. It is important to distinguish the booster phenomenon from a true tuberculin conversion. The booster effect occurs in a person previously infected with *Mtb* but who has a false-negative skin test; repeat skin test elicits a truly positive test. Conversion (not to be confused with the booster phenomenon) occurs in persons previously uninfected with *Mtb* and who have had a true negative tuberculin skin test, but who become infected within 2 years as demonstrated by a repeat skin test induration that is a positive 10 mm or more during this period. Several factors influence the results and interpretation of the PPD skin test. Decreased skin test reactivity is associated with waning DTH with time, disseminated TB, corticosteroids and other drugs and other diseases in addition to the elimination of TB infection. False-positive PPD results occur with cross-reactions with non-tuberculous mycobacteria and in persons receiving the Bacillus Calmette–Guérin (BCG) vaccine, the latter having been administered to some foreign-born elderly persons, which has an unpredictable effect on the PPD skin test reactivity and is presumed to wane after 10 years. The use of anergy testing has been debated because of lack of a standardized protocol for selection of the number and type of antigens to be used, the criteria for defining positive and negative reactions and administration and interpretation techniques.[23]

Interferon-gamma release assays

In 2005, the CDC published guidelines for using an interferon gamma release assay (IGRA) known as the QuantiFERON-TB Gold test (QFT-G) (Cellestis, Carnegie, Victoria, Australia).[24] Subsequently, two new IGRAs were approved by the US Food and Drug Administration (FDA) as aids in diagnosing both TB infection and disease. These tests are the QuantiFERON-TB Gold In-Tube test (QFT-GIT) (Cellestis) and the T-SPOT.TB test (T-Spot) (Oxford Immunotec, Abingdon, UK). The antigens, methods and interpretation criteria for these assays differ from those for IGRAs approved previously by the FDA. This *in vitro* test measures by an enzyme-linked immunosorbent assay (ELISA) the concentration of interferon-gamma (IFN-γ) released from tuberculin PPD sensitized lymphocytes in heparinized whole blood incubated for 16–24 h. Interpretation of QFT results is stratified by estimated risk for *Mtb* infection in a manner similar to the tuberculin skin test using different induration cut-off values.

Although data on the accuracy of IGRAs and their ability to predict subsequent active TB are limited, to date no major deficiencies have been reported in studies involving various populations.

The role for QFT in targeted testing has not yet been clearly defined and may be a useful alternative to tuberculin skin testing in the future for all infected individuals including the elderly.

Chest radiography

Chest radiography is indicated in all individuals with suspected TB infection, regardless of the primary site of infection. In the elderly, 75% of all TB disease occurs in the respiratory tract and largely represents reactivation disease; 10–20% of cases may be as a result of primary infection.[25] Although reactivation TB disease characteristically involves the apical and posterior segments of the upper lobes of the lungs, several studies have shown that many elderly patients manifest their pulmonary infection in either the middle or lower lobes or the pleura, and also present with interstitial, patchy or cavitary infiltrates that may be bilateral. Primary TB can involve any lung segment, but more often tends to involve the middle or lower lobes in addition to mediastinal or hilar lymph nodes. Therefore, caution must be exercised in dismissing the radiographic diagnosis of pulmonary TB in the elderly because of the atypical location of the infection in the lung fields.

Laboratory diagnosis

Sputum samples must be collected from all patients, regardless of age, with pulmonary symptoms or chest radiographic changes compatible with TB disease and who have not been previously treated with antituberculous agents. In elderly patients unable to expectorate sputum, other diagnostic techniques such as sputum induction or bronchoscopy should be considered. Flexible bronchoscopy to obtain bronchial washings and to perform bronchial biopsies has been shown to be of diagnostic value for TB disease in the elderly; however, in frail and very old patients, the risk of such a procedure must be carefully balanced against the benefits of potentially making a definite diagnosis of TB.[26] In the case of pulmonary and genitourinary TB, three consecutive early-morning sputum or urine specimens, respectively, are recommended for routine mycobacteriological studies. Sputum samples are examined initially by smear before and after concentration and then cultured for *Mtb*. Because routine mycobacterial culture methods may require up to 6 weeks for growth of *Mtb*, many laboratories now use radiometric procedures for the isolation and susceptibility testing of this organism; this method may identify the organisms as early as after 8 days. Sterile body fluids and tissues can be inoculated into liquid media, which also allow the growth and detection of *Mtb* 7–10 days earlier than in the solid media techniques. Histological examination of tissue from various sites such as the liver, lymph nodes, bone marrow, pleura or synovium may show the characteristic tissue reaction (caseous necrosis with granuloma formation) with or without AFB, which would also strongly support the diagnosis of TB disease. Other diagnostic methods for TB that have been clinically evaluated include serology and nucleic acid amplification (NAA) tests such as polymerase chain reaction (PCR) and other methods for amplifying DNA and RNA.[27] The latter may facilitate rapid detection of *Mtb* from respiratory specimens; the interpretation and use of the NAA test results has been updated by the CDC. Similar techniques using DNA probes can be used to track the spread of the organism in epidemiological studies and may be used to predict drug resistance prior to the availability of standard results; such methods are currently being used in some laboratories. The rapid diagnosis of TB is especially important in elderly patients, in addition to HIV-infected persons and patients with multidrug-resistant (MDR) TB.

Treatment

Treatment of TB disease

The recommended treatment regimens are for the most part based on evidence from clinical trials and are rated on the basis of a system developed by the United States Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA).[28] There are four recommended regimens for treating patients with TB caused by drug-susceptible organisms. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances, which are described subsequently. Each regimen has an initial phase of 2 months followed by a choice of several options for the continuation phase of either 4 or 7 months. The recommended treatment algorithm and regimens are shown in Figure 115.1 and Table 115.1, respectively.[28] Because of the relatively high proportion of adult patients with TB caused by organisms that are resistant to isoniazid (INH), four drugs are necessary in the initial phase for the 6 month regimen to be maximally effective. Thus, in most circumstances, the treatment regimen for all adults including the elderly with previously untreated TB should consist of a 2 month initial phase of INH, rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB). If (when) drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included. If PZA cannot be included in the initial phase of treatment or if the isolate is resistant to PZA alone (an unusual circumstance), the initial phase should consist of INH, RIF and EMB given daily for 2 months. However, since most TB in the elderly is due to reactivation (from infection acquired prior to 1950), the organism will generally be sensitive to INH and other antituberculous drugs.

Treatment of MDR-TB is complex and often needs to be individualized, requiring the addition of a minimum

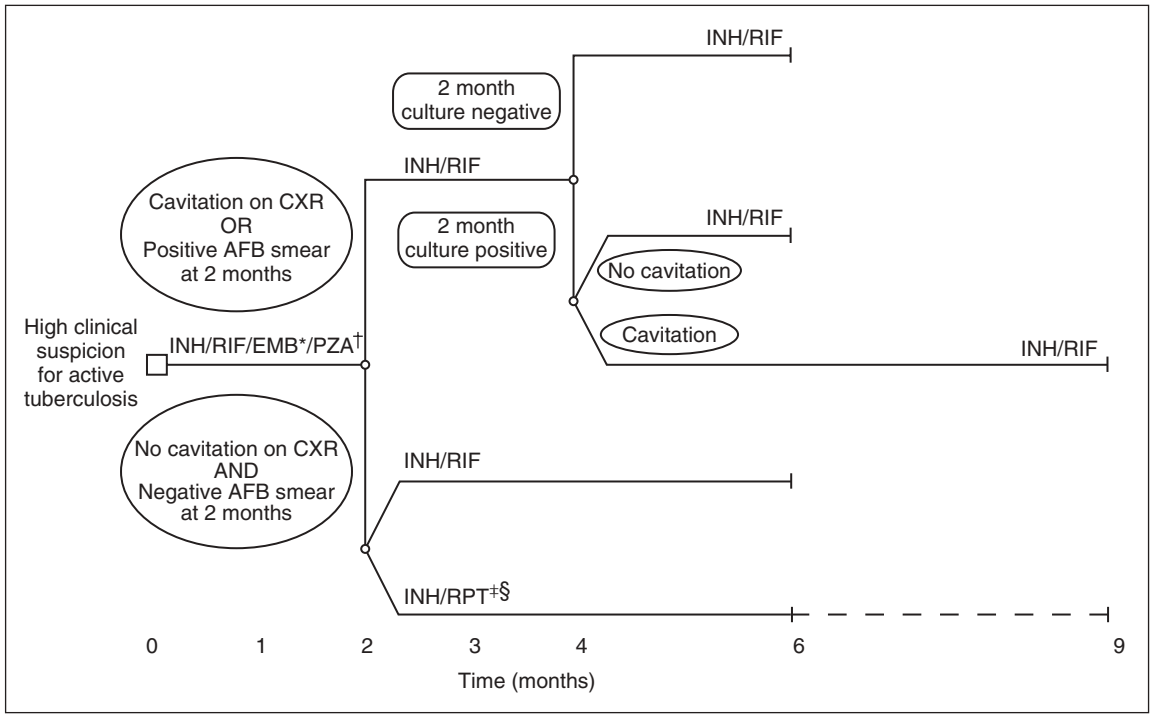

Figure 115.1 Treatment algorithm for tuberculosis. Patients in whom tuberculosis is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at the time of completion of 2 months of therapy is positive, the continuation phase should be lenghened to 7 months (total of 9 months of treatment). If the patient has HIV infection and the $CD4^+$ cell count is <100 per μl, the continuation phase should consist of daily or three times weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once weekly isonizaid and rifapertine, or daily or twice weekly isoniazid and rifampin, to complete a total of 6 months (bottom). Patients receiving isoniazid and rifapentine, and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months). EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance. PZA may be discontinued after it has been taken for 2 months (56 doses). RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis. Therapy should be extended to 9 months if 2-month cultures is positive. CXR, chest radiiograph; EMP, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine. (Source: Centers for Disease Control and Prevention, American Thoracic Society and Infectious Disease Society of America.[28])

of two additional antituberculous agents to which the organism is presumably susceptible, preferably in consultation with a TB expert who is familiar with *Mtb* drug resistance. Alternative drugs such as capreomycin, kanamycin, amikacin, ethionamide and cycloserine, and also the newer quinolones, may have to be used for treatment in such cases.

Monitoring of response to drug therapy

Patients with active pulmonary TB should be monitored on a monthly basis with sputum examination until conversion to negative by culture is achieved; this usually occurs within 3 months in 90% of cases. Continued positive sputum cultures for *Mtb* beyond 3 months of initiation of therapy should raise the suspicion for drug resistance or non-compliance (if not on DOT); such patients should have sputum culture and susceptibility repeated and started on DOT pending results of these data. Follow-up chest radiography is indicated 2–3 months after initiation of drug therapy. Older patients are at greater risk for hepatic toxicity from INH. Although INH therapy poses a small but significant risk for hepatitis, the hepatitis is relatively low in frequency and mild in severity. Therefore, presumably with careful monitoring of the older patient, antituberculous chemotherapy is a relatively safe intervention in this population. It is recommended that clinical assessments and also baseline liver function tests be performed before the administration of INH and RIF (and PZA) in older patients.

Table 115.1 Tuberculosis disease treatment regimens.[28]

Initial phase			Continuation phase				Rating[d] (evidence)[e]	
Regimen	Drugs[a]	Interval and doses[b] (minimal duration)	Regimen	Drugs[a]	Interval and doses[b,c] (minimal duration)	Range of total closes (minimal duration)	HIV−	HIV+
1	INH RIF PZA EMB	7 days per week for 56 doses (8 wk) or 5 days per week for 40 doses (8 wk)[f]	1a	INH/RIF	7 days per week for 126 doses (18 wk) or 5 days per week for 90 doses (18 wk)[f]	182–130 (26 wk)	A(I)	A(II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A(I)	A(II)[h]
			1c[g]	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B(I)	E(I)
2	INH RIF PZA EMB	7 days per week for 14 doses (2 wk),[f] then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk),[f] then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A(II)	B(II)[h]
			2b[g]	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B(I)	E(I)
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	3a	INH/RIF	3 times weekly for 54 doses (18 wk)	78 (26 wk)	B(I)	B(II)
4	INH RIF EMB	7 days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)[f]	4a	INH/RIF	7 days per week for 217 doses (31 wk)	273–195 (39 wk)	C(I)	C(II)
			4b	INH/RIF	or 5 days per week for 155 doses (31 wk)[f] Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C(I)	C(II)

[a]EMB, Bhambutol; INH, isoniazide; PZA, pyrazinnarnidel; RIF, rifampin; RPT, rifapentine.

[b]When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be and effective practice.

[c]Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month [31 week; either 217 doses (daily) or 62 doses (twice weekly)] continuation phase.

[d]Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be give; E = should never be given.

[e]Definitions of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

[f]Five-day-a-week administration is always given by DOT. Rating for 5 days per week regimens is A III.

[g]Not recommended for HIV-infected patients with CD4 + cell counts <100 cells per μl.

[h]Options 1c and 2b should be used only in HIV-negative patients who have negative sputurn smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograpah (see text). For patients started on this regiment and found to have a positive culture from the 2-month specimen, treatment should be extended and extra 3 months.

Monthly clinical evaluations and periodic measurements of the serum aminotransferase (SGOT) level should be performed in the elderly. If the SGOT rises to five times above normal or if the patient exhibits symptoms or signs of hepatitis, INH (and also other hepatotoxic drugs) should be discontinued. After clinical symptoms improve or the SGOT level normalizes, or both, INH may be resumed at a lower dose (e.g. 50 mg kg^{-1} per day) and gradually increased to a full dose if symptoms and the SGOT level remain stable. In case of relapse of the hepatitis with the INH challenge, the drug should be replaced with an alternative regimen. There is some disagreement among clinicians regarding the monitoring of liver function tests in older patients on INH. Because frail, elderly patients may often be asymptomatic in the presence of worsening hepatitis and may not be able to communicate symptoms, laboratory monitoring seems prudent. The frequency of such monitoring (e.g. monthly or every 2–3 months) remains less clear. RIF, in addition to hepatitis, is also associated with orange discoloration of body fluids.

EMB may cause loss of colour discrimination, diminished visual acuity and central scotomata; older patients receiving this drug should have frequent evaluation of visual acuity and colour discrimination. Streptomycin is associated with irreversible auditory and vestibular damage and generally should not be prescribed in the elderly. Adverse effects of PZA include hyperuricaemia, hepatitis and flushing. Dose adjustment of antituberculous drugs is necessary with streptomycin, when used in the presence of renal impairment; however, no adjustment is needed for INH, RIF or PZA in most elderly patients.

Treatment of latent TB infection

Table 115.2 outlines the revised criteria for positive tuberculin skin test reactivity by size of induration requiring drug treatment.[29] Drug therapy for latent TB (based on tuberculin skin test reactivity) considerably decreases the risk of progression of TB infection to TB disease. Since the LTBI treatment recommendations address adults in general, targeted skin testing and treatment of high-risk populations can be applied to the elderly. The INH daily regimen for 9 months has recently replaced the previously recommended 6 month schedule for treatment of LTBI. Randomized, prospective trials in HIV-negative persons have indicated that a 12 month regimen is more effective than 6 months of treatment; subgroup analyses of several trials indicate that the maximum beneficial effect of INH is likely.

In a community-based study conducted in Bethel, Alaska, persons who took <25% of the prescribed annual dose had a threefold higher risk for TB than those who took more than 50% of the annual dose. In addition, the efficacy decreased significantly if INH was taken for less than 9 months. In instances of known exposure to drug-resistant organisms, alternative preventive therapy regimens may be recommended.

Although these recommendations do not specifically address ageing adults, the concept of targeted skin testing and revised LTBI treatment guidelines for high-risk populations to include the elderly can be applied. Elderly persons receiving isoniazid should continue to be monitored for hepatitis and peripheral neuropathy induced by the drug.

Table 115.2 Skin test criteria for positive tuberculin reaction (mm induration).[29]

≥5 *mm*
1 HIV-positive persons
2 Recent contacts of person(s) with infectious tuberculosis
3 Persons with chest radiographs consistent with tuberculosis (e.g. fibrotic changes)
4 Patients with organ transplants and other immunosuppressed hosts receiving the equivalent of >15 mg per day of prednisone for >1 month
≥10 *mm*
1 Recent arrivals (<5 years) from high-prevalence countries
2 Injection-drug users
3 Residents and employees of high-risk congregate settings: prisons, jails, nursing homes, other healthcare facilities, residential facilities for AIDS patients and homeless shelters
4 Mycobacteriology laboratory personnel
5 High-risk clinical conditions: silicosis; gastrectomy; jejunoileal bypass; ≥10% below ideal body weight; chronic renal failure; diabetes mellitus; haematological malignancies (e.g. lymphomas, leukaemias); other specific malignancies (carcinoma of the head or neck and lung) (alcoholics are also considered high risk)
≥15 *mm*
1 Persons with no risk factors for TB

Infection control issues

The primary goal of an infection control programme is to detect TB disease early and to isolate and treat persons with infectious TB promptly. Prevention of transmission of TB in any healthcare environment is of the utmost importance, for both patients and healthcare workers. Enhanced awareness of drug-resistant TB has prompted public health agencies to institute strict TB identification, isolation, treatment and prevention guidelines. The TB infection control programme in most acute care and long-term care facilities should consist of three types of control measures: administrative actions (i.e. prompt detection of suspected cases, isolation of infectious patients and rapid institution of appropriate treatment), engineering control [negative-pressure ventilation rooms, high-efficiency particulate air (HEPA) filtration and ultraviolet germicidal irradiation (UVGI)] and personal respiratory protection requirements (masks). The Advisory Committee for the Elimination of Tuberculosis of the CDC has established recommendations for surveillance, containment, assessment and reporting of TB infection and disease in long-term care facilities; healthcare professionals, administrators and staff of such extended care programmes should be made aware of these recommendations.[30]

Key points

- Tuberculosis (TB) remains one of the world's most lethal infectious diseases.
- Preventive and control strategies among other high-risk groups such as the elderly remain a challenge.
- Clinical features of TB in older adults may be atypical and confused with age-related diseases.
- Underlying diseases, malnutrition and biological changes with ageing can contribute to age-associated decline in cellular immune responses to infecting agents such as *Mycobacterium tuberculosis*.
- Diagnosis and management of TB in the elderly may be difficult; treatment can be associated with adverse drug reactions.
- The institutionalized elderly are at high risk both for reactivation of latent TB and to new TB infection.

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CHAPTER 116

Valvular heart disease and infective endocarditis

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Introduction

Valvular heart disease (VHD) is an increasingly common and important problem despite the decline of rheumatic fever. One of the principal reasons is the relative and absolute ongoing increase in the elderly population, such that the increased requirements for care of degenerative valve disease now outweigh the decreasing burden of rheumatic heart disease.

The widespread availability of echocardiography has revolutionized investigation by providing accurate and non-invasive assessment of severity and a means of monitoring disease progression, while also allowing progress in the application of interventional techniques and reconstructive valve surgery. The indications for valve replacement surgery have been broadened by improvements in prosthetic valve design and reduced perioperative mortality while the advent of transcatheter aortic valve implantation (TAVI) and percutaneous mitral valve repair offer a less invasive alternative for elderly patients whose frailty and comorbidity may preclude conventional surgery.

Epidemiology and pathophysiology

VHD was historically caused by rheumatic fever and this remains a major burden in developing countries. However, industrialized countries face a different type of problem: as rheumatic disease has fallen substantially due to improved living conditions and the introduction of penicillin for streptococcal pharyngitis in the 1940s, degenerative VHD is increasingly common.

With an ever-increasing elderly population over the past half century and the increasing availability of diagnostic tools such as echocardiography, the requirements for care of degenerative valve disease now outweigh the decreasing burden of rheumatic heart disease.

Prevalence of valvular heart disease in an ageing population

The prevalence data for VHD in the elderly are derived mainly from European and North American studies. In 2006, Nkomo *et al.*[1] collated the results of several large population-based studies (total >28 000 adults) to assess the overall prevalence of VHD and its effect on overall survival in the general population of the USA. The prevalence of VHD increased with age, rising from 0.7% in those aged 18–44 years to 13% in those over 75 years of age (Figure 116.1). The most common valve lesion was mitral regurgitation, followed closely by aortic stenosis, whilst mitral stenosis was very uncommon in this population. There was equal gender preponderance. The presence of VHD also had a statistically significant impact on survival, emphasizing its significance as a healthcare issue.

There is also a demonstrable association between the prevalence of VHD and increasing age. In the developed world, low birth rates and increasing life expectancy have inverted the age pyramid. All adult age groups below 65 years will begin to diminish in size throughout most of Europe beyond 2030. In contrast, those aged over 65 years are expected to grow to 107 million by 2025 and 133 million by 2050, with a 180% (19 million to 51 million) increase in those over 80 years of age between 2005 and 2050. Based on a prevalence of VHD of 13% in the over-75 age group, this will result in over 6.5 million new cases of moderate to severe VHD in Europe by 2050.

In the UK, approximately 1 million individuals over 65 years of age are thought to be affected by VHD. This will inevitably increase rapidly as the UK population aged >75 years is projected to rise by ~50% by 2025. In turn, the impact on healthcare resources is likely to grow substantially.

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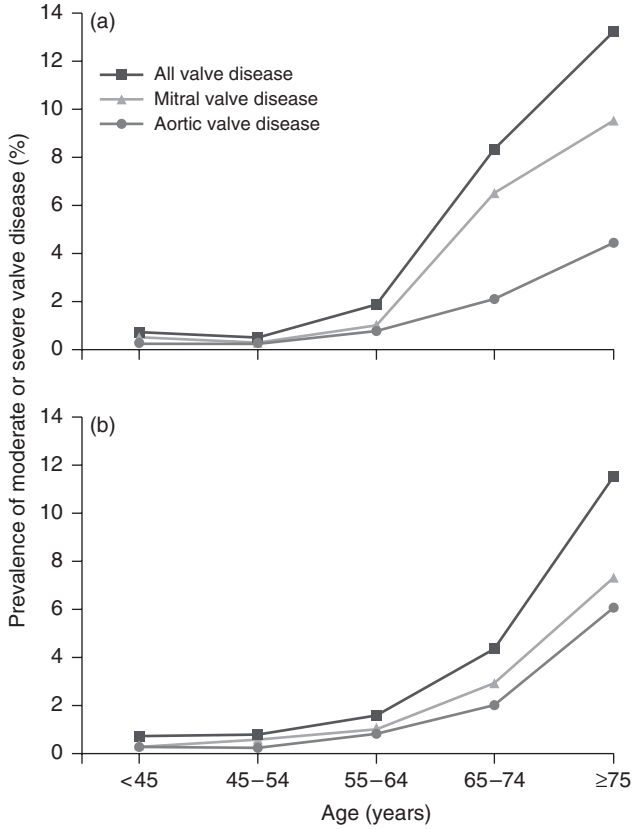


Figure 116.1 The rising prevalence of valvular heart disease according to age. Frequency in (a) population-based studies and (a) the Olmsted County community.[1]

Aetiology of valvular heart disease

The aetiology and management of VHD were assessed across Europe in 2001 in the European Society of Cardiology Euro Heart Survey on Valvular Heart Disease. Prospective data were collected on 5000 patients with significant primary VHD (according to specific criteria) or infective endocarditis, in both in- and outpatient settings across cardiology and cardiothoracic departments in Europe.

In this hospital setting, the most common native left-sided valve lesion was aortic stenosis (43%), followed by mitral regurgitation (32%), aortic regurgitation (13%) and mitral stenosis (12%). The dominant aetiology of aortic stenosis, aortic regurgitation and mitral regurgitation was degenerative, while mitral stenosis resulted from rheumatic disease in 85%. Valvular regurgitation was caused by a wider range of aetiologies than stenosis, with endocarditis and congenital abnormalities featuring prominently in aortic regurgitation and ischaemia an important cause of mitral regurgitation.

Aortic stenosis

Detection of aortic stenosis in the elderly has increased with improved diagnostic tools. Echocardiography has revealed mild calcification of the aortic valve in up to 40% of those aged 60 years or over and 75% of those aged over 85 years. The overall prevalence of clinically significant aortic stenosis in those older than 70 years has become more frequent and is ~1–3%. Recent evidence suggests variation in the left ventricular response to aortic stenosis according to gender: whereas elderly males tend to undergo ventricular dilatation with systolic impairment, females have small, hypertrophied ventricles with preserved contractile function.

Overall, the most common cause of aortic stenosis is a congenitally bicuspid aortic valve, accounting for over 40% of UK cases (Figure 116.2a). Rheumatic aortic stenosis is now much rarer. Bicuspid valves occur in 0.5–2.5% of the general population and are more common in males. Significant stenosis, caused by progressive calcification (Figure 116.2b and 116.2c), develops in up to one-third of affected individuals, often before the age of 70 years.

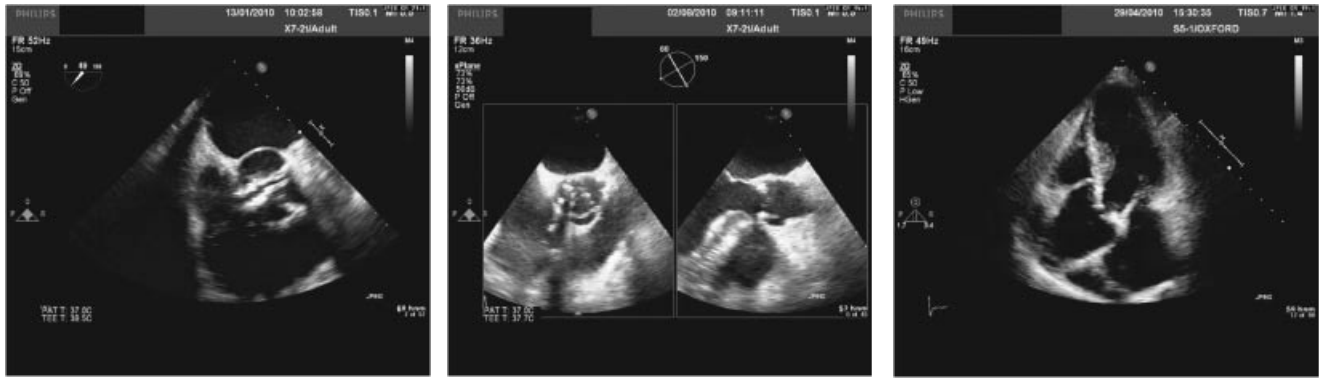
Aortic sclerosis (thickening of the aortic valve without obstruction) is present in 25% of patients over 65 years of age and is associated with age, hypertension, smoking, male gender, low-density lipoprotein levels and diabetes mellitus. Nearly 9% of these patients progress to aortic stenosis over a 5 year period.

Senile degeneration of an anatomically normal aortic valve is increasingly important in the ageing population. The degeneration is related to repeated minor trauma to the valve cusps leading to fibrosis and deposition of calcium, with consequent immobility and stenosis. These changes are unusual before the age of 70 years but the incidence increases rapidly thereafter.

Aortic stenosis is the result of impaired mobility of the valve cusps, leading to reduced systolic excursion and open valve area (normally 3–4 cm^2). The consequence is an increase in left ventricular systolic pressure and a pressure gradient across the valve between the ventricle and aorta. The ventricle subsequently attempts to accommodate this pressure increase through hypertrophy that in turn leads to falling compliance of the left ventricle. Symptoms of exertional breathlessness, angina and syncope eventually result. Most patients develop these symptoms before a reduction in ejection fraction, but some present with poor ventricular function and overt heart failure.

Aortic regurgitation

Aortic regurgitation is less common than aortic stenosis with a prevalence of <1% in the elderly population. The



(a) (b) (c)

Figure 116.2 (a) Transoesophageal echocardiogram (TOE) demonstrating severe aortic stenosis in a bicuspid valve with left ventricular dilatation. (b, c) TOE demonstrating a severely calcified tricuspid aortic valve.

usual aetiology is aortic root dilatation, which appears to occur as part of normal ageing and is more frequent in hypertensive patients. Of the valvular causes, bileaflet valves comprise ~60% of cases, infective endocarditis 20% and rheumatic heart disease <10%. Rarer causes include inflammatory aortitis (associated with rheumatoid arthritis, ankylosing spondylitis, giant-cell arteritis and syphilis), aortic root aneurysm and 'silent' chronic dissection. Acute aortic regurgitation is less common and is usually due to infective endocarditis, but may occasionally arise as a result of aortic dissection, dehiscence of a valve prosthesis or trauma.

Aortic regurgitation is caused by inability of the valve cusps to coapt during the diastolic phase of the cardiac cycle. This may be due to an abnormality of the aortic root or a problem with the valve itself that disrupts valve closure. As a result, a proportion of left ventricular stroke volume (>50% in severe cases) leaks back through the aortic valve in diastole, inducing a compensatory response of ventricular hypertrophy to maintain efficient ventricular function. This compensatory response eventually becomes inadequate, resulting in progressive ventricular dilatation and the onset of exertional breathlessness.

Mitral stenosis

The falling incidence of mitral stenosis parallels that of acute rheumatic fever. Rheumatic scarring and inflammation of the valve and subvalvular tissues eventually lead to progressive fibrosis, calcification and stenosis, which usually becomes haemodynamically significant in the fourth and fifth decades.

The major cause of mitral stenosis worldwide is rheumatic fever, usually developing within a few years of acquiring the disease. In contrast, congenital abnormalities of the valve make up a larger proportion of cases in industrialized nations. The stenotic valve is the result of fusion, thickening and reduced mobility of the mitral leaflets and chordae tendinae. Valve area decreases from the normal of around 4 cm^2 to less than 1 cm^2, producing a diastolic gradient between the left atrium and left ventricle, raised left atrial pressure (and consequent enlargement), secondary pulmonary hypertension and right heart failure. The primary symptom is breathlessness on exertion.

Mitral regurgitation

The most common cause of mitral regurgitation in the elderly UK population is myxomatous degeneration. The prevalence appears to be ~2% with a 5:1 male preponderance and an even age distribution. It mainly affects the posterior mitral valve leaflet to cause chordal stretching (and ultimately rupture).

Mitral regurgitation is also a common accompaniment to ischaemic heart disease as a result of ventricular dilatation and papillary muscle dysfunction; ~50% of patients have some degree of mitral regurgitation 1 month after suffering a myocardial infarction. Acute papillary muscle rupture may complicate myocardial infarction to cause acute mitral regurgitation, which may also result from infective endocarditis or dehiscence of a prosthetic valve.

Mitral annular calcification is a common echocardiographic finding which occurs more often in women and affects 8.5–10% of the population above the age of 50 years (although affected individuals are usually much older). In one-third there is associated mitral regurgitation, but this is usually mild and asymptomatic; accompanying mitral

stenosis is rare. Other complications are unusual, although there is an associated t2–3-fold increase in the incidence of embolic stroke. Mitral valve prolapse is also frequently detected by echocardiography, although diagnostic criteria vary. Its clinical relevance is often uncertain although in some cases it may be the antecedent of a 'floppy valve' where the chordae are grossly elongated, the valve voluminous and mitral regurgitation more significant.

Pulmonary/tricuspid valve disease

The elderly population rarely presents with primary disease of these valves and there are no meaningful epidemiological data available. Pulmonary hypertension associated with mitral valve disease can cause regurgitation of either or both right heart valves. Tricuspid stenosis may be associated with rheumatic mitral and aortic valve disease and is occasionally seen as a feature of carcinoid syndrome.

History and clinical assessment

Despite technological advances in the investigation and management of cardiovascular disease, an accurate history and careful clinical assessment remain the most important part of diagnosis and management in the elderly. Questioning may be more difficult and it is often necessary to enlist the help of a relative or other carer. This history should seek a background or rheumatic fever, ischaemic heart disease or hypertension and incorporate specific enquiry for symptoms of dyspnoea (either on exertion or at rest, particularly when lying flat) and exertional angina or syncope. However, symptoms in the elderly are often vague and difficult to interpret, particularly if there is concomitant pulmonary or cerebral disease.

The principles of examination are the same as those for any other age group and the weight of the patient and a dental inspection should be routinely included. However, in elderly patients many of the classical manifestations of VHD may be attenuated by the effects of ageing on the cardiovascular system, namely atherosclerosis, hypertension and valve calcification. Thus, for example, a pulse of normal character or the presence of systemic hypertension do not exclude significant aortic stenosis in the elderly. Conversely, a wide pulse pressure is not necessarily indicative of aortic regurgitation. Inspection of the jugular venous pressure is of particular importance as dependent oedema secondary to chronic venous insufficiency is common and may erroneously suggest circulatory overload. Systolic murmurs are common in the elderly and have been reported in up to 60% of normal subjects. They are frequently due to increasing rigidity and calcification of the aortic cusps without significant obstruction or mild mitral regurgitation through a floppy valve. Diastolic murmurs are always abnormal and usually indicate aortic regurgitation or mitral stenosis, although the customary accompanying opening snap in mitral stenosis may be absent in the elderly due to valve calcification.

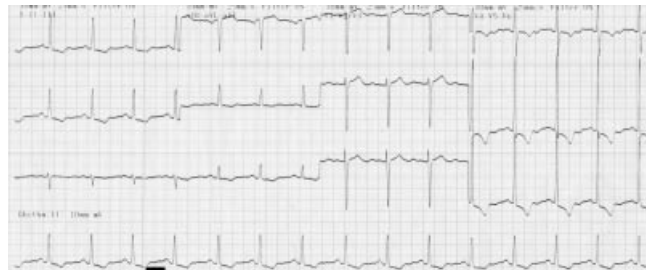


Figure 116.3 ECG demonstrating left ventricular hypertrophy: increased amplitude of the QRS complex, ST-segment depression and T-wave inversion in the lateral and inferior leads.

Investigations

Electrocardiogram (ECG)

This provides important information regarding heart rate and rhythm. The ECG has low sensitivity for the detection of atrial or ventricular hypertrophy and therefore assessment of the severity of valve lesions from the ECG should be cautious (Figure 116.3). Similarly, ST/T wave changes may result from left ventricular hypertrophy or the use of digoxin and do not necessarily indicate the presence of coexisting coronary artery disease.

Chest X-ray

A chest X-ray is useful for the assessment of heart size, the identification of specific chamber enlargement (particularly the left atrium) or aortic dilatation and for detection of pulmonary vascular changes or oedema (Figure 116.4). It can also assist in localizing valve calcification and prosthetic valves, particularly if a lateral radiograph is requested. Finally, the detection of coincident pulmonary disease may be of considerable clinical importance in some cases, especially if invasive investigation is being considered. The cardiothoracic ratio may increase to 60% as part of normal ageing, particularly beyond 75 years, caused by a small increase in cardiac diameter and a larger fall in chest diameter. Hence the use of absolute dimensions may be more appropriate in this age group: a transverse cardiac diameter >15 cm usually indicates significant enlargement.

Echocardiography

This is now the technique of choice for the diagnosis and evaluation of VHD and has negated the need for routine cardiac catheterization in many patients. It provides information regarding valve anatomy and physiology in addition to the effect of valve abnormality on cardiac function and allows serial observation of the patient over time.

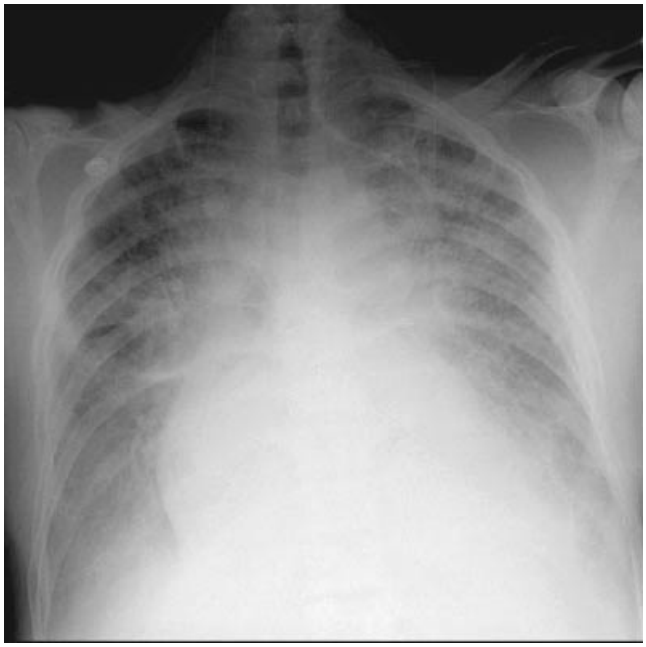


Figure 116.4 Chest X-ray demonstrating pulmonary oedema: cardiomegaly, alveolar shadowing, upper lobe diversion and blunting of the costophrenic angles.

Interpretation can be difficult and requires experience, particularly in the Doppler assessment of valve stenosis when poor signal alignment may lead to underestimation of the peak velocity. Furthermore, it is a sensitive tool and 'physiological' regurgitation is often detected in normal subjects.

There are three principal modalities: M (or motion)-mode, two-dimensional (or cross-sectional) and Doppler echocardiography. M-mode employs a single stationary beam of ultrasound to produce a recording of motion along a single line through the heart and provides a large amount of accurate information allowing the determination of cavity dimensions and wall thickness and physiological measurements of wall motion. Two-dimensional echocardiography images a plane through the heart by sweeping a beam of ultrasound though the sector of interest and is the modality of choice for displaying anatomy (Figure 116.5). Standardized precordial views are employed and a further subcostal view may be invaluable in elderly patients, in whom obesity, lung disease, chest wall deformities or kyphoscoliosis may preclude conventional imaging. Doppler echocardiography permits accurate assessment of the position, direction and velocity of the blood flow within the heart. This information can be anatomically correlated by superimposing a colour flow Doppler map onto the two-dimensional image. Three-dimensional imaging is under development and allows reconstruction of cardiac anatomy, which may be of particular value when percutaneous intervention or surgery is being considered.

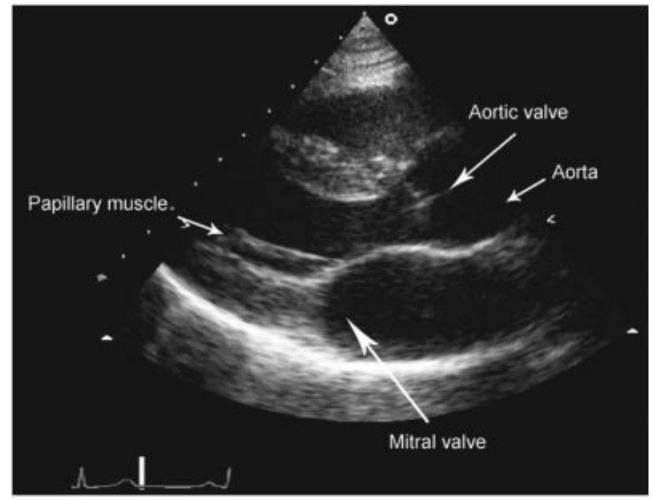


Figure 116.5 Parasternal long-axis TTE demonstrating the left ventricular cavity and mitral and aortic valves.

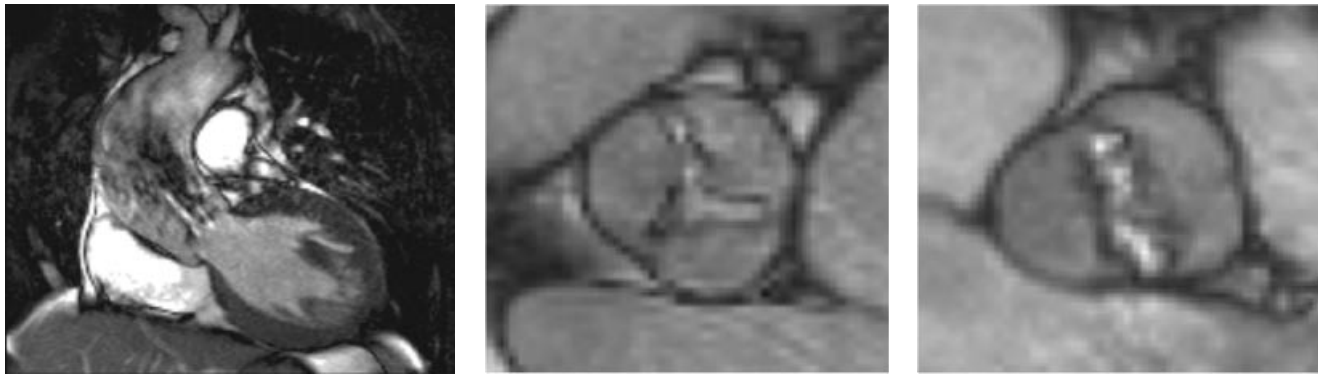
Transoesophageal echocardiography is a specialized technique which provides excellent image quality in almost every patient. The procedure is tolerated well by the elderly and may be performed on an outpatient basis, usually under light sedation. It has specific indications in the assessment and management of VHD and is highly sensitive in the detection of thrombus, vegetations and abscesses which may not be apparent on precordial imaging.

Cardiac catheterization

The increasing sophistication of echocardiography means that invasive investigations are unnecessary in many patients. Nevertheless, specific questions may remain, most commonly the presence or absence of coronary artery disease in patients being considered for valve surgery. The mortality of the procedure is 0.1–0.2% and other complications (cardiac or vascular trauma, embolism, arrhythmias or contrast reactions) occur in ~1% of cases. Patients at higher risk include the elderly and those with poor left ventricular function, severe aortic stenosis, pulmonary hypertension or peripheral vascular disease. As much information as possible should be obtained using non-invasive techniques to ensure that any invasive investigation is not unnecessarily prolonged. Furthermore, in the emergency setting, coronary angiography should not delay a potentially life-saving operation, such as emergency aortic valve replacement. In these situations, the investigations required should be decided by consultation between the physician and the surgeon and, if necessary, performed on the way to the operating theatre.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) is becoming more frequently used in the assessment of VHD. It provides



(a) (b) (c)

Figure 116.6 Cardiac magnetic resonance imaging in aortic stenosis. (a) A narrow high-velocity jet in the left ventricular outflow tract; (b) 'en-face' view of a stenosed trileaflet aortic valve; (c) 'en-face' view of a stenosed bicuspid aortic valve.

quantitative and reproducible measures of both stenosis and regurgitation, and also accurate measurement of the volume and function of both ventricles (Figure 116.6). A unique feature of CMR is the ability to measure flow through an image slice, with good agreement between invasive measurements and *in vitro* testing, allowing the quantification of regurgitation rather than a qualitative assessment of severity. The aortic root and ascending aorta are also accurately assessed and are important aspects in aortic valve disease. CMR can thus provide a comprehensive and accurate evaluation of the severity of VHD and the consequences for the ventricles. Detailed information on valve leaflet anatomy is less well assessed, however, and transoesophageal echocardiography provides higher resolution imaging.

Measurement of forward and reverse flow across the aortic or pulmonary valves allows the quantification of aortic/pulmonary regurgitation, providing both regurgitant volume and fraction. The high mobility of the mitral and tricuspid valves and turbulent flow across them makes direct flow measurement difficult. In valve stenosis, valve area can be assessed by direct planimetry rather than by calculation and usually provides a better assessment of severity with CMR than velocity across the valve – velocity measurements lack the spatial and temporal resolution of Doppler echocardiography and may underestimate valve severity. Left ventricular mass can also be measured accurately, in addition to volumes and function.

At present, the limited availability of CMR restricts its use in VHD and it has a relatively high cost compared with echocardiography. Acquisition and analysis times are also longer, making it less attractive for outpatient use, although developments in scanners and software technology are likely. Arrhythmias (e.g. atrial fibrillation) may impair image quality and affect the accuracy of flow measurements, although newer imaging sequences can cope with this common problem. Claustrophobic patients can often be scanned by experienced personnel, though about 1–2% of patients may find this too difficult. CMR remains mostly contraindicated in the presence of certain ferromagnetic implants, including cerebral aneurysm clips and cardiac pacemakers/defibrillators. However, prosthetic (including metallic) valves and coronary stents are almost never a problem.

Cardiac computed tomography

Although cardiac computed tomography (CT) is increasingly used in the context of coronary artery disease, its use in VHD is limited. It can provide morphological information on the valves and their associated structures (particularly calcification) and also volume and mass measurements. However, it does not provide haemodynamic information, is sensitive to arrhythmias and requires a slow heart rate (often necessitating beta-blockade or other rate-slowing medication). CT also involves ionizing radiation, although newer scanners utilize techniques to reduce the dose significantly. A major future advantage of CT may be the non-invasive exclusion of coronary artery disease prior to valve surgery.

Aortic stenosis

Symptoms and signs

The normal aortic valve area is 3–4 cm^2 and symptoms of haemodynamic origin, namely syncope, angina and dyspnoea, usually develop when this falls to 1–1.5 cm^2. The onset of symptoms heralds a poor prognosis (Figure 116.7) with a 1 year mortality of 43%. In the elderly, coexisting cerebral or coronary artery disease may make interpretation difficult. Furthermore, many patients with severe aortic stenosis may be asymptomatic and the diagnosis is easily overlooked.

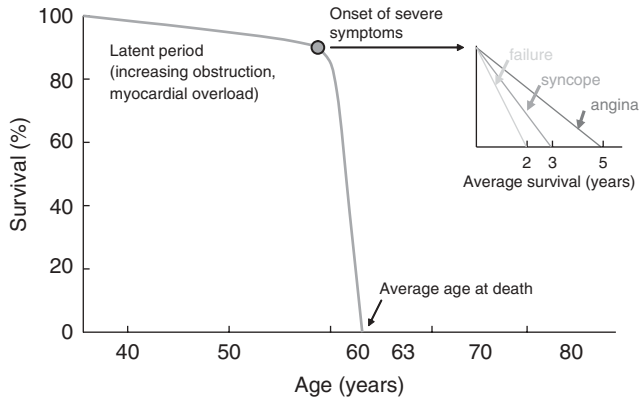


Figure 116.7 The natural history of aortic stenosis demonstrating a long asymptomatic preclinical phase followed by rapid decline associated with poor prognosis following the onset of symptoms.

Syncope, usually associated with exercise, becomes increasingly likely as disease progresses and is associated with an increased incidence of sudden death. The underlying mechanism is probably related to inappropriate vasodilatation secondary to abnormal baroreceptor sensitivity stimulated by elevated left ventricular pressure. In the presence of outflow obstruction, the compensatory increase in cardiac output is limited and cerebral hypoperfusion results.

Angina occurs in two-thirds of patients with aortic stenosis. Contributing factors include myocardial hypertrophy, prolonged systole and high left ventricular pressure, and these are compounded if there is coexisting coronary artery disease. The incidence of associated coronary artery disease increases with age and the need for concomitant coronary artery bypass grafting at the time of aortic valve replacement rises from 20% at 70 years to more than 60% at ages >80 years.

The onset of dyspnoea indicates significant left ventricular impairment. This is associated with a very poor prognosis and is an indication for urgent surgical intervention.

The classical peripheral manifestations of aortic stenosis (a plateau pulse and narrow pulse pressure) are often absent in elderly patients because the pulse waveform is distorted by stiff, atherosclerotic vessels. A normal or elevated blood pressure does not exclude the diagnosis. In many cases, the only physical sign is the presence of a mid systolic murmur which is usually squeaking or musical in character, loudest at the base of the heart, and typically radiates into the neck. In practice, the intensity of the murmur is a poor guide to the severity of the stenosis and in elderly patients its position is often atypical (frequently maximal at the apex). There may be an accompanying thrill and the apex beat is forceful and sustained. The first heart sound is usually normal and an ejection click (associated with a mobile valve) is uncommon in older patients. The aortic component of the second sound may be diminished (or absent) and delayed because of reduced valve mobility and the prolonged ejection time.

The finding of a systolic murmur in conjunction with any of the above symptoms should not be dismissed without further assessment. Given the high prevalence of aortic valve disease in the elderly, the poor prognosis of symptomatic aortic stenosis, the benefits of valve replacement and the difficulty of making precise clinical diagnosis, such patients require echocardiography.

Investigations

The ECG and chest X-ray

A normal ECG and chest X-ray do not exclude the diagnosis. The ECG usually shows left ventricular hypertrophy with repolarization changes; anteroseptal Q waves, occurring most often when there is left-axis deviation, are not unusual and may be mistakenly ascribed to a previous myocardial infarction. Occasionally, conducting tissue calcification can cause atrioventricular or bundle branch block. In the elderly, calcification of the stenosed aortic valve is invariably present on the chest X-ray, particularly in the lateral view. There may be post-stenotic aortic dilatation and cardiac enlargement and pulmonary oedema develop in the late stages.

Echocardiography

Two-dimensional and Doppler echocardiography are the techniques of choice for the assessment of suspected aortic stenosis. Aortic valve thickening and calcification are common in the elderly and associated restriction of cusp mobility is required to confirm the diagnosis. In practice, heavy calcification often obscures visualization of the valve structure and disease severity can only be determined by continuous-wave Doppler echocardiography. Echocardiography also provides the most convenient assessment of ventricular hypertrophy, size and function.

The velocity (V) of blood flow across the valve can be measured by continuous-wave Doppler echocardiography and, using the modified Bernoulli equation, the *peak instantaneous* pressure gradient can be derived (gradient $= 4V^2$). Generally, there is an excellent correlation between the gradients measured using invasive and non-invasive techniques although the *peak-to-peak instantaneous* gradient is usually higher than the *peak-to-peak* gradient measured at cardiac catheterization. A Doppler gradient >70–80 mmHg (equivalent to a catheter gradient of 50 mmHg) indicates significant aortic stenosis (Figure 116.8).

However, the gradient produced by any degree of valve obstruction is smaller if cardiac output falls due to declining left ventricular function. Conversely, the severity of aortic stenosis will be overestimated in the presence of any

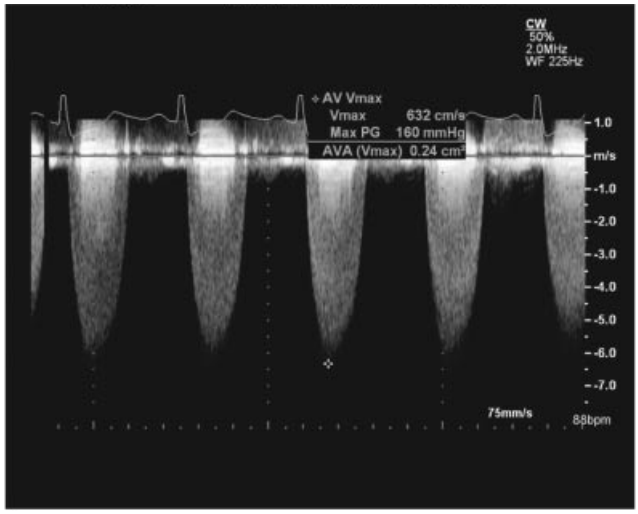


Figure 116.8 Continuous-wave Doppler echocardiography in severe aortic stenosis – the peak velocity is nearly 6 m s^{-1} (equivalent to a trans-valve pressure gradient of ~140 mmHg).

associated aortic regurgitation when the peak velocity is elevated by the large forward stroke volume. Hence clinical assessment is particularly important in these patients.

Cardiac catheterization

As outlined, invasive assessment of the aortic valve by cardiac catheterization is no longer necessary for most patients. In complicated cases, where echocardiography is equivocal or inconsistent, catheterization may be needed to resolve diagnostic doubt, particularly if cardiac output is low. The stenotic valve may be crossed retrogradely or the left ventricle entered trans-septally from the left atrium and aortic and left ventricular pressures measured simultaneously. In most patients, the major purpose of catheterization is to detect concomitant coronary artery disease (present in 50% of cases) prior to aortic valve replacement.

Aortic regurgitation

Symptoms and signs

In chronic aortic regurgitation, the left ventricle dilates and becomes hypertrophied – even when severe, the effective forward stroke volume remains normal. The end-diastolic volume increases but end-systolic volume is initially maintained. Eventually, the end-diastolic pressure rises, systolic function declines and only then does exercise tolerance fall. Thus, symptoms of exertional dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea usually follow a long asymptomatic period. Angina is less frequent than in aortic stenosis and its presence is strongly suggestive of coexisting coronary artery disease. Syncope is rare. In acute regurgitation, adaptive processes do not come into play and circulatory failure rapidly results.

The pulse pressure is wide with increased systolic and low diastolic pressure, although these signs may be obscured in the elderly by concomitant hypertension and a rigid circulation. During blood pressure measurement, the Korotkoff sounds can often be heard right down to zero although diastolic pressure is usually no lower than 30 mmHg. The apex is displaced laterally and inferiorly and is hyperdynamic. A high-pitched decrescendo early diastolic murmur is typically heard maximally in the third or fourth left intercostal space. In general, the duration of the murmur is a better guide to the severity of regurgitation than its intensity. Finally, there may be a loud ejection murmur secondary to increased forward flow during systole (not necessarily indicative of associated aortic stenosis) and a low-pitched mid-diastolic (Austin Flint) murmur due to fluttering and partial closure of the anterior mitral valve leaflet caused by the regurgitant jet. Clinical signs may be less obvious in acute aortic regurgitation – there is usually a prominent gallop rhythm and the typical murmur may be inaudible.

Investigations

The ECG and chest X-ray

The ECG characteristically shows left ventricular hypertrophy or, less often, left bundle branch block. Cardiomegaly on the chest X-ray is due to left ventricular enlargement. Ascending aortic dilatation is common and often extensive, particularly if there is additional aortic stenosis or if regurgitation is secondary to aortic wall disease.

Echocardiography

Although sensitive in detection, echocardiography is of only moderate value in quantitating valvular regurgitation. The appearances of the aortic valve and root may provide clues to the aetiology and serial measurements of left ventricular dimensions guide clinical decisions in conjunction with the patient's symptoms.

High-frequency fluttering of the anterior mitral valve leaflet in diastole is pathognomonic of aortic regurgitation and is best seen with M-mode imaging. Colour flow Doppler echocardiography is the more sensitive method of detection and clinically insignificant regurgitation may be found in a sizeable proportion of elderly patients. The extent to which the regurgitant jet extends from the aortic cusps into the left ventricle and its width in the left ventricular outflow tract are both useful measures of severity (Figure 116.9). Poor prognostic signs in acute severe aortic regurgitation are premature mitral valve closure (caused by free regurgitation into a non-compliant ventricle) and

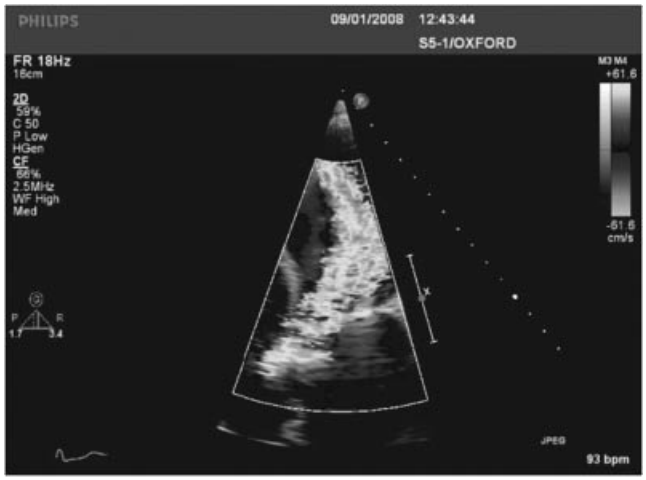


Figure 116.9 Apical five-chamber TTE view demonstrating a wide jet of severe aortic regurgitation in the left ventricular outflow tract extending to the left ventricular apex. See plate section for a colour version of this image.

premature aortic valve opening, caused by the rapid rise in left ventricular diastolic pressure.

Transoesophageal echocardiography provides useful supplementary information regarding the aetiology of aortic regurgitation and is invaluable in the assessment of aortic dissection.

Cardiac catheterization

The diagnosis and severity of aortic regurgitation are usually evident from clinical and echocardiographic assessment, although aortography may provide extra information if root replacement is being considered. As in aortic stenosis, coronary angiography is the main purpose of invasive investigation.

Cardiac magnetic resonance

This is the best technique for the assessment of pathology in the aortic root and arch and is therefore used increasingly in patients with aortic dilatation or dissection, particularly if surgery is planned. If unavailable, then CT is a useful substitute.

Prognosis and treatment

Chronic aortic regurgitation, even if severe, is associated with a good prognosis: with medical treatment alone, 75% of patients survive 5 years and 50% 10 years after diagnosis. The onset of symptoms heralds rapid deterioration and heart failure is usually associated with death within 2 years. Therefore, the early detection of left ventricular dysfunction is of paramount importance.

The progression of disease and need for surgery may be delayed by vasodilators (e.g. nifedipine) in asymptomatic patients with normal left ventricular contraction. Intervention on prognostic grounds alone does not improve outcome in the elderly and surgery for the symptom-free patient is not currently recommended. Unless there are specific contraindications, vasodilator therapy should be given to all elderly patients with aortic regurgitation. This treatment is usually all that is required in the very elderly and those unsuitable for surgery. Otherwise, patients should be monitored frequently (approximately 6 monthly) and serial echocardiographic assessment of left ventricular size and function undertaken. The onset of symptoms associated with evidence of progressive left ventricular dilatation (end-systolic dimension >5.5 cm) or reduced ejection fraction (<50%) indicates the need for surgery. Aortic valve replacement is nearly always necessary in the elderly, although occasionally the native valve can be resuspended, for example, in aortic dissection. Some patients with coexisting aneurysmal dilatation of the ascending aorta (>5.5 cm) may require aortic root replacement.

In patients with severe, long-standing left ventricular impairment, the prognosis is poor and the choice between medical and surgical management is extremely difficult. Left ventricular function may improve following aortic valve replacement, particularly if symptoms are mild and the duration of left ventricular dysfunction is short. However, the operative risk is high (>10%) and in many patients there is no postoperative improvement. Therefore, patients in this category, particularly with other risk factors for surgery, are probably best managed with vigorous medical therapy.

Acute aortic regurgitation requires emergency surgery and interim reduction of afterload using intravenous vasodilators.

Mitral stenosis

Symptoms and signs

The normal mitral valve orifice is 4 cm^2. In severe mitral stenosis this may be reduced to less than 1 cm^2, associated with pulmonary hypertension and raised pulmonary vascular resistance. In mild–moderate disease the cardiac output may remain normal but is unable to increase with exercise, leading to exertional dyspnoea. With more severe degrees of stenosis, cardiac output becomes subnormal, even at rest. Symptoms may also be precipitated during tachycardia (when abbreviation of diastole is associated with impaired left ventricular filling) and by the onset of atrial fibrillation when cardiac output may fall by 20–25% due to loss of atrial transport.

Older patients with mitral stenosis tend to fall into two categories: those with restenosis after a previously successful surgical mitral valvotomy and those with more slowly progressive rheumatic disease which has only become

symptomatic in later life. Only 40–65% of patients give a history of rheumatic fever. The symptoms are a combination of exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, cough, palpitations and fatigue. These usually arise in the fourth or fifth decade and may remain mild for many years before gradual, often unnoticed, deterioration. Indeed, the diagnosis may not be made until echocardiography is performed to investigate unexplained breathlessness. Occult mitral stenosis is also an important cause of embolic stroke.

The classical signs of mitral stenosis are often absent in the elderly. A malar flush is uncommon and the signs associated with a pliable valve (tapping apex beat, loud first heart sound and opening snap) are unusual because the valve has calcified and become immobile. Auscultation reveals an apical rumbling mid-diastolic murmur; presystolic accentuation is rare as most are in atrial fibrillation. In general, the length of the murmur is proportional to the severity of the lesion, although it is often difficult to hear in its entirety. In advanced disease, signs of pulmonary hypertension may be present: raised venous pressure, right ventricular heave, loud pulmonary second sound, murmurs of pulmonary and tricuspid regurgitation and dependent oedema.

Investigations

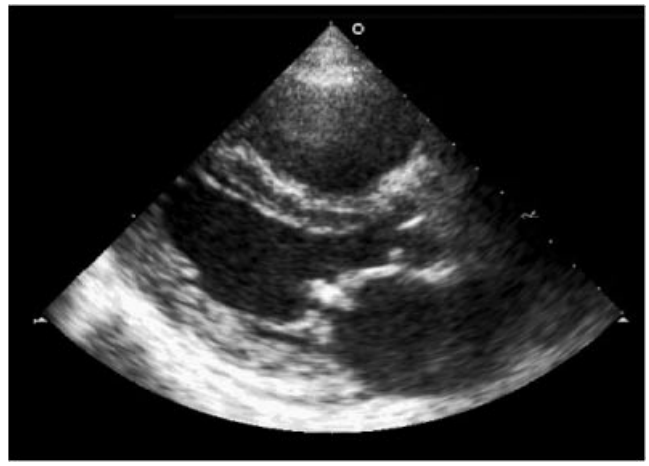
The ECG and chest X-ray

In sinus rhythm, a broad, notched P wave illustrates left atrial enlargement, although atrial fibrillation is more usual. The development of right ventricular hypertrophy is associated with right-axis deviation and may ultimately cause a prominent R wave in lead V1.

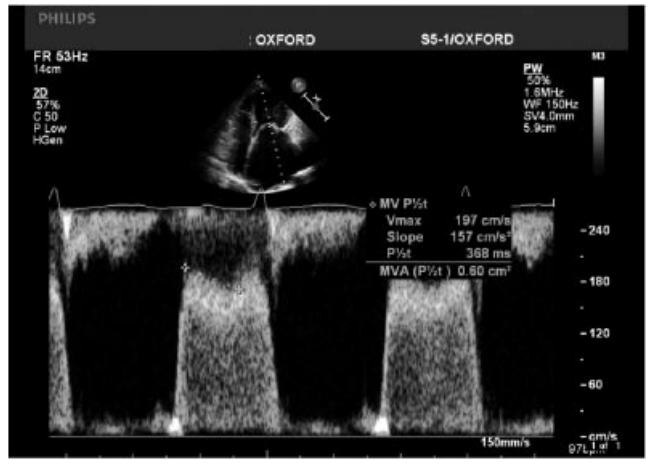
The chest X-ray reveals enlargement of the left atrium and its appendage, causing a double right heart border and widening of the tracheal bifurcation (best seen on a penetrated film). Gross left atrial dilatation usually indicates additional mitral regurgitation. Calcification of the valve, best appreciated on a lateral view, is common and usually indicates long-standing disease. Ultimately, signs of pulmonary venous and arterial hypertension develop and pulmonary oedema may be present.

Echocardiography

In rheumatic mitral stenosis, the valve leaflets are thickened and usually calcified with commissural fusion (Figure 116.10a). Cusp mobility is reduced and bowing of the leaflets occurs in diastole. Associated features such as left atrial enlargement and/or thrombus, pulmonary hypertension and mitral regurgitation may also be apparent. The valve area can be calculated from the two-dimensional image using planimetry, although this is subject to error. A more accurate assessment is obtained by measuring the velocity of flow across the valve using



(a)



(b)

Figure 116.10 (a) TTE parasternal long-axis view in diastole demonstrating thickened and calcified mitral valve leaflets. (b) The pressure half-time may be estimated by tracing the mitral inflow deceleration slope at 368 ms (severe >220 ms).

continuous-wave Doppler echocardiography. By this means, a pressure half-time (the time interval for the velocity to fall from its peak value to the peak value divided by the square root of 2, normal <100 ms) can be derived (Figure 116.10b) and the valve area calculated with the following equation:

$$\text{mitral valve area (cm}^2) = 220/\text{pressure half-time (ms)} \quad (116.1)$$

Tricuspid regurgitation is usually present to some extent and measurement of the velocity of the jet allows estimation of the pulmonary artery pressure.

Transoesophageal imaging may have an additive role in examining the anatomy of the valve and subvalvar apparatus and in excluding the presence of left atrial thrombus. This is important prior to balloon mitral valvuloplasty

or DC cardioversion and in the investigation of systemic embolism.

Cardiac catheterization

Although echocardiographic imaging has removed the need for diagnostic catheterization in most cases, right and left heart studies may still be indicated when there is persistent uncertainly in determining disease severity or in patients with multiple valve lesions and/or coexisting pulmonary disease. Assessment of the coronary arteries is indicated in those being considered for interventional treatment.

Prognosis and treatment

Patients may remain asymptomatic for decades. Progression is variable after the onset of symptoms but generally occurs over a 5–10-year period with a 20% 5-year and 40% 10-year mortality for those treated medically. Systemic thromboemboli (most frequently to the cerebral circulation) occur in 20% of patients. Infective endocarditis is relatively unusual.

Most elderly patients with mitral stenosis are in atrial fibrillation and can be improved by good control of the ventricular response. The treatment of choice is digoxin and verapamil is a useful adjunctive therapy. Amiodarone is almost always effective but has many side effects and should be reserved for resistant cases. Beta-blockers also serve a useful role, even in helping to maintain sinus rhythm, and are under-utilized. In cases where atrial fibrillation is of short duration and the left atrium is not significantly enlarged (<4.5 cm on echocardiography), cardioversion should be considered, although this is contraindicated when there is evidence of left atrial thrombus.

Diuretics may be necessary for the control of breathlessness, but high doses may cause volume depletion and should be avoided. Anticoagulation is recommended for all patients with mitral stenosis, especially if there is left atrial enlargement, and is mandatory in those with atrial fibrillation (unless there are obvious contraindications). It reduces the risk of stroke by 60%, although the risk of bleeding is increased, especially in patients over 80 years of age.

All patients who remain symptomatic despite medical treatment should be considered for percutaneous balloon mitral valvuloplasty; the surgical alternatives are open mitral commissurotomy or mitral valve replacement.

Mitral regurgitation

Symptoms and signs

In chronic mitral regurgitation, the impedance to flow from the left ventricle into the left atrium is low and therefore the ventricle is relatively spared from the effects of chronic volume overload. Initially, left ventricular end-diastolic volume is normal, but as time passes the ventricle dilates, develops hypertrophy and ultimately fails. Symptoms can therefore be delayed for years and may only develop after deterioration in left ventricular function has already occurred. In contrast, those with acute regurgitation become unwell suddenly and may deteriorate rapidly.

The main complaints are of chronic fatigue, lethargy and progressive dyspnoea. Some may present with pulmonary oedema and fluid retention. The signs of mitral regurgitation are relatively unaffected by age. The pulse volume is normal and may have a sharp character and the apex beat is heaving and displaced laterally. The murmur is pansystolic, often with a marked crescendo towards the second heart sound, and is heard loudest at the apex radiating to the axilla (although radiation to the base of the heart or carotid arteries frequently accompanies posterior leaflet prolapse). A third heart sound is common. In acute mitral regurgitation, a sinus tachycardia and systemic hypotension are invariable. The apex beat is hyperdynamic but undisplaced unless there has been preceding chronic mitral regurgitation. The apical systolic murmur is harsh and there is often an accompanying thrill. A gallop rhythm may be palpable and signs of pulmonary oedema are usually present.

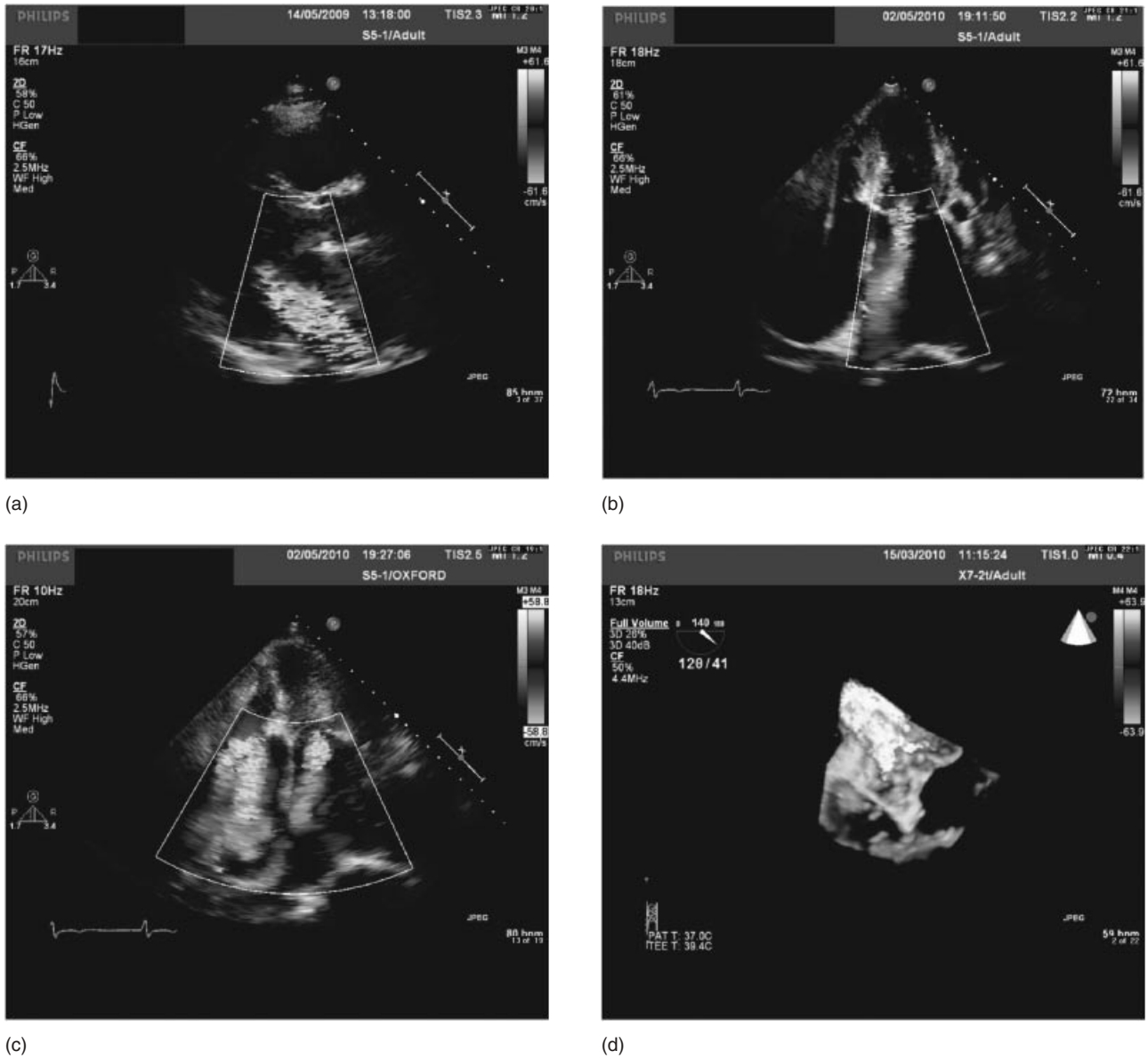
Investigations

The ECG and chest X-ray

The ECG shows left atrial enlargement or atrial fibrillation. Left ventricular hypertrophy occurs in ~50% of patients. In chronic mitral regurgitation, the chest X-ray shows left ventricular and left atrial dilatation. Calcification of the mitral annulus is best seen in the lateral projection. In acute mitral regurgitation, the heart size is normal and there is usually gross pulmonary oedema.

Echocardiography

Echocardiography demonstrates the enlarged left atrium, the anatomy of the sub-valvar apparatus and may indicate the aetiology of mitral regurgitation (Figure 116.11). Pulsed Doppler and colour flow mapping can detect the most trivial degree of regurgitation and demonstrate its direction. They also provide semiquantitative indices of severity although interpretation is highly subjective and notoriously unreliable. Therefore, assessment may be difficult. Left ventricular dimensions and wall motion are useful clues: in severe regurgitation there is dilatation and vigorous contraction characteristic of volume overload. Quantitative assessment is possible but remains a relatively specialized tool. In practice, it remains common to grade regurgitation as mild, moderate or severe according to the width of the regurgitant colour jet as it enters the left atrium and to base management decisions on left ventricular size and function in conjunction with the patient's symptoms.



(a) (b)

(c) (d)

Figure 116.11 (a) TTE parasternal long-axis view with a broad colour jet across the mitral valve demonstrating severe mitral regurgitation. (b) TTE apical view demonstrating severe mitral regurgitation; the broad colour jet occupies over one-third of the left atrium. (c) TTE apical view demonstrating torrential tricuspid regurgitation and concurrent severe mitral regurgitation, causing biatrial dilatation. (d) 3D TOE demonstrating severe mitral regurgitation. See plate section for a colour version of this image.

Transoesophageal echocardiography provides more information regarding valvular morphology and the mechanism of regurgitation. These are of particular importance preoperatively, especially when valve repair rather than replacement is being considered.

Cardiac catheterization

Catheterization is rarely needed for diagnostic purposes but coronary angiography is mandatory in those patients being considered for surgery. Left ventricular angiography can be used to assess left ventricular function and end-diastolic pressure and right heart catheterization may confirm the presence of associated pulmonary hypertension.

Prognosis and treatment

Mitral regurgitation may remain indolent for many years and therefore the timing of invasive investigations is difficult in the elderly. Asymptomatic patients have a 5-year survival rate of >80%, but when symptoms develop this falls

to 45%. In chronic regurgitation these may be initially controlled by vasodilators (particularly angiotensin-converting enzyme inhibitors), diuretics and digoxin, but such medical therapy should not be used as a tool to defer surgery in suitable candidates. Those with left atrial enlargement and atrial fibrillation should be anticoagulated; in sinus rhythm the risk of thromboembolism is relatively small and treatment with aspirin alone may be adequate.

Surgical treatment improves survival in symptomatic mitral regurgitation and outcome is related to ventricular function; thus, the combination of symptoms and echocardiographic evidence of progressively increasing left ventricular size (end-systolic dimension >5.5 cm) suggests the need for mitral valve replacement or repair. Age *per se* is not a contraindication to surgery, but advanced left ventricular dysfunction in patients who present late may make the risks unacceptably high.

In acute mitral regurgitation, the outlook with medical therapy alone is bleak. Even in elderly patients, intra-aortic balloon counter pulsation should be considered in addition to standard measures (oxygen, intravenous diuretics, vasodilators and inotropes) in order to improve the haemodynamic situation while patients undergo emergency cardiac catheterization followed by mitral valve surgery and revascularization if appropriate. The operative mortality is high (>50%).

Mixed valve disease

Assessment and treatment comprise a summation of the factors for each individual valve lesion. Some combinations bear a poor prognosis, for example, mitral stenosis and aortic regurgitation, and such patients require careful monitoring. The risk of combined aortic and mitral valve replacement is significantly higher than for single valve replacement, with reported mortality rates of 15–30% in the elderly. Clearly, this may influence the decision to proceed. Occasionally, the need for surgery can be avoided by a 'palliative' balloon procedure, particularly if pure mitral stenosis is the major component, although this decision should only be made after specialist assessment and multidisciplinary team discussion.

Interventional treatment in the elderly

The age of patients undergoing valvular heart surgery in the UK continues to rise and there has been an increase in the number of procedures in which coronary artery bypass grafting and valve surgery are combined (Figure 116.12). More than 20% of patients currently treated by cardiac surgery are over the age of 75 years and 5% are over 80 years old. Overall perioperative mortality in this age group is falling, from 5% in 2004 to 3.4% in 2008. Not only has the risk of surgery diminished, but medium-term survival rates are also remarkably good; for a patient aged 75 years, the 5-year survival following isolated valve surgery is 70%.

General considerations

Risk assessment

When surgical intervention is being considered, it is important to optimize medical therapy, which may warrant specialist referral. For some patients this will improve symptoms sufficiently to avoid the need for intervention and its associated risk.

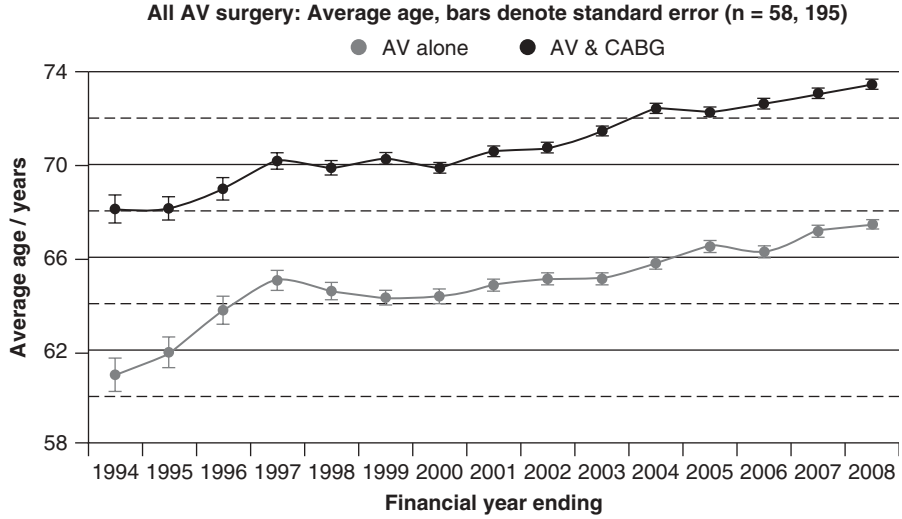


Figure 116.12 The rising age of patients undergoing aortic valve (AV) surgery in the UK. CABG = concomitant coronary artery bypass grafting. Data reproduced from the Sixth National Adult Cardiac Surgical Database Report, Society for Cardiothoracic Surgery in Great Britain and Ireland.

Operative mortality is higher in the elderly and also greater following valve surgery than with coronary artery bypass grafting alone. Nevertheless, with judicious patient selection, early referral and optimization of preoperative status, the results of valve replacement in the elderly can approach those in younger patients. Factors influencing outcome include concomitant coronary artery disease, poor left ventricular function, associated tricuspid valve disease (often associated with pulmonary hypertension), cerebrovascular or peripheral vascular disease, impaired respiratory or renal function, osteoporosis and general frailty, patient motivation, nutritional status and previous or coexisting malignant disease. Of particular concern are pre-existing cardiac, respiratory or renal impairment and neurological status, as these systems are most susceptible to the detrimental effects of cardiopulmonary bypass. There are several risk stratification models that can be used to estimate overall perioperative risk, the best known being the EuroSCORE and the Society of Thoracic Surgeons risk score.

The failure to deal with significant associated coronary disease is now recognized as a frequent cause of early and late mortality following otherwise successful valve replacement and preoperative coronary angiography is an important investigation in the elderly prior to consideration of valve surgery. However, the principle of a simple, quick procedure in the elderly patient is important; additional bypass grafting should only be undertaken for severe coronary artery disease. Urgent or emergency surgery has a higher mortality (often >30%) and the risk is also magnified if second-time surgery (for example, aortic valve replacement following coronary artery bypass grafting some years previously) is being considered.

Complications

The incidence of perioperative myocardial infarction after open heart surgery is usually estimated at around 2–4%. Atrial fibrillation is common preoperatively in patients with VHD but frequently develops *de novo* between the second and fourth postoperative day, especially in the elderly. Treatment with digoxin or amiodarone is usually successful and cardioversion may be required for the small proportion of patients who are haemodynamically compromised.

Major focal neurological abnormalities occur in around 1% of patients undergoing valve replacement and the risk is increased in the elderly (4% in patients over the age of 85 years). Neuropsychological abnormalities can be identified in 30–50% of patients following cardiopulmonary bypass but the majority are subtle and resolve within a few months of surgery. Cardiac surgery results in some degree of respiratory impairment in virtually all patients, but particularly in the elderly patient whose respiratory reserve is already diminished. The overall incidence of acute renal failure requiring dialysis is around 5%, although some degree of reversible renal dysfunction occurs in up to one-third of patients.

Aortic valve disease

Elective surgical valve replacement is the treatment of choice for the management of severe aortic valve disease. In the elderly the procedure can be undertaken with a mortality rate of 2–10%. Long-term outcome is good with late survival rates similar to age- and gender-matched control populations. In general, valve replacement for aortic regurgitation has a less favourable outcome than for aortic stenosis since patients tend to present at a later stage when irreversible left ventricular damage has occurred. Preoperative left ventricular impairment is not a definite contraindication to surgery (particularly in aortic stenosis) but an ejection fraction of <45% is associated with considerably increased operative risk. This risk also rises with increasing age and if valve replacement is combined with coronary artery bypass grafting.

Balloon aortic valvuloplasty (BAV) is a percutaneous technique using a large balloon catheter to dilate a stenosed aortic valve and has been shown to increase aortic valve area, reduce the trans-valve gradient and improve symptoms. However, BAV does not alter the natural history of severe aortic stenosis; symptoms usually recur within a few months and the procedure does not reduce overall mortality or increase long-term survival. Despite this, there are some clearly defined situations where the technique can be considered:

- Bridge to definitive treatment [either open aortic valve replacement or TAVI (Figure 116.13)].
- Bridge to new technology, for example, for those patients whose aortic annulus is too large for the currently available TAVI devices.
- Adjunct to pre-TAVI percutaneous coronary intervention (PCI) (which is often complex and high risk in the setting of severe aortic stenosis).
- Therapeutic trial – particularly in breathless patients with a combination of severe aortic stenosis, significant coronary artery disease and severe airways disease.
- Palliative – although this is more controversial, some feel that offering 3–6 months of symptomatic benefit to very elderly patients (even when recurrence of symptoms is likely) is worthwhile in some clinical scenarios.
- In patients requiring urgent non-cardiac surgery (e.g. for malignancy).

Recently, percutaneous TAVI has become available as another treatment option for patients who are unsuitable or considered too high risk for conventional surgery. In this procedure, which avoids the need for sternotomy or cardiopulmonary bypass, a stent-mounted bioprosthetic aortic valve is deployed within the diseased native aortic valve after predilatation with a valvuloplasty balloon, via the

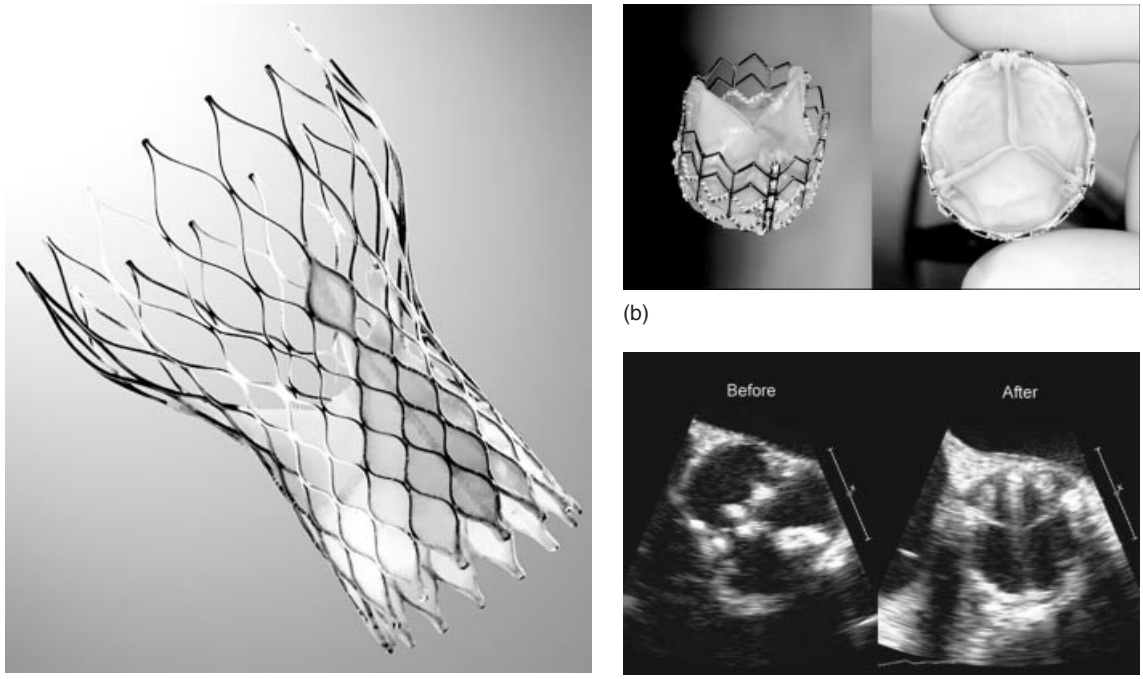


Figure 116.13 Contemporary transcatheter aortic valve implantation devices: (a) Medtronic Corevalve; (b) Sapien–Edwards. (c) TOE images before and after deployment of the Sapien–Edwards TAVI prosthesis.

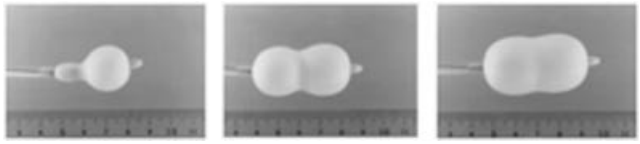
femoral, subclavian or apical route. In high-risk patients, TAVI has been shown to be superior to standard medical management (including BAV). Although 30 day mortality in patients undergoing TAVI is higher, 1-year cardiovascular mortality is 20% for TAVI patients compared with 42% for standard medical management alone or in conjunction with BAV.

Mitral valve disease

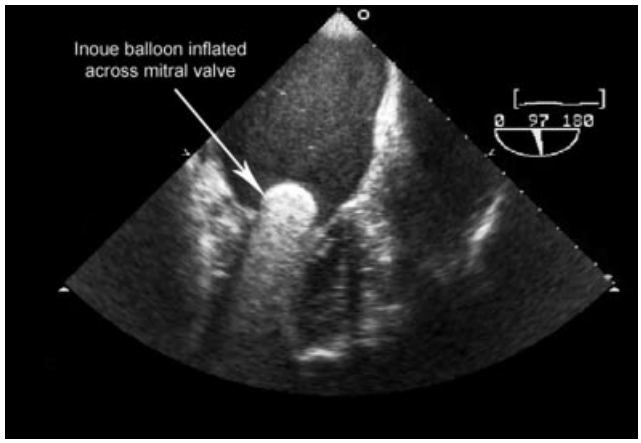
The most common indication for mitral valve intervention in the elderly is mitral regurgitation, whether caused by degenerative or functional mitral valve disease. Patients undergoing mitral valve replacement have a higher perioperative and long-term mortality than those undergoing aortic valve replacement, probably as a consequence of associated left ventricular impairment and pulmonary hypertension. Mortality for elective mitral valve replacement in the elderly is ~15% and this risk is increased if there is associated coronary artery disease or significant left ventricular impairment.

In patients with mitral regurgitation, there is now accumulating evidence of the benefits of mitral valve repair rather than replacement. Valve repair results in better preservation of left ventricular function and may obviate the need for anticoagulation. Compared with valve replacement, mitral repair is associated with lower mortality (5.5 versus 15.6% in one series), reduced risk of stroke and shorter duration of intensive care stay. The procedure is well established in elderly patients and earlier intervention may be favoured if repair is thought to be technically feasible, particularly if mitral regurgitation is due to ischaemic annulo-papillary dysfunction or non-rheumatic disease. Transoesophageal echocardiography is essential for pre- and perioperative assessment and can predict the probability of a successful repair procedure. The role of conservative surgery in rheumatic mitral regurgitation is limited due to poor long-term event-free survival.

Percutaneous balloon mitral valvuloplasty for rheumatic mitral stenosis was originally described by Inoue *et al*.[2] in 1984 and is well established as a less invasive replacement for surgical valvotomy (Figure 116.14). In this procedure, a cylindrical balloon is positioned across the mitral valve and inflated to split the fused commissures. The balloon is waisted to minimize movement during balloon inflation. Mitral valve area and gradient can then be measured and a further inflation carried out in a stepwise approach if required. Although ideally suited to those with pliable, non-calcified valves, there is now increasing evidence that it can be performed safely in the elderly with less suitable valve morphology and in those who have undergone surgical valvotomy in the past. The procedure usually results in a moderate but significant improvement in valve function associated with a clinically useful symptomatic result. The



(a)



(b)

Figure 116.14 (a) The Inoue balloon used during percutaneous balloon mitral valvuloplasty. (b) TOE demonstrating balloon inflation across the stenosed mitral valve.

procedural mortality of 3% in the elderly is considerably less than with mitral valve replacement. Contraindications include the presence of left atrial thrombus, severe subvalvar involvement or valve calcification and significant mitral regurgitation. These can be detected by preprocedural evaluation with transoesophageal echocardiography which is mandatory. The procedure usually increases mitral valve area by $\sim 1.0\,cm^2$ associated with an improvement in functional class. Complications include severe mitral regurgitation requiring emergency surgery (<1% of cases), cardiac perforation and restenosis (which is considerably slower and less frequent than after BAV).

Percutaneous options for the treatment of mitral regurgitation are now emerging and two approaches are currently under investigation. One technique for the surgical repair of mitral regurgitation is to suture the central portions of the two leaflets of the mitral valve together (the Alfieri stitch) to create a double orifice of smaller area than the original valve defect. The Mitraclip system has been developed to recreate this procedure using a percutaneous approach and initial results suggest that this may be a useful minimally invasive method for mitral repair (Figure 116.15). Percutaneous mitral valve annuloplasty is an alternative technique for the management of functional mitral regurgitation where an annuloplasty ring is deployed via the coronary sinus, thereby reducing mitral annular size and the degree of mitral regurgitation.

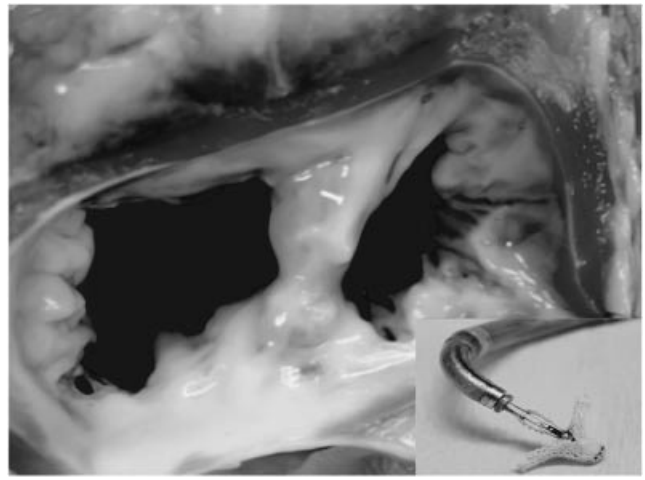


Figure 116.15 The percutaneous Evalve Mitraclip device (inset) provides a central tether for the opposing mitral valve leaflets thereby creating a double orifice and reducing the regurgitant area, as demonstrated in this *ex vivo* porcine model.

Prosthetic valves in the elderly

Choice of prosthesis

There are two broad categories of valve prosthesis that can be used for surgical valve replacement: mechanical valves and bioprostheses (xenograft). In rare cases (usually related to infective endocarditis affecting the aortic valve), alternatives include a human homograft or pulmonary autograft (transplanting the native pulmonary valve to the aortic position and implanting a homograft in the pulmonary position; the Ross procedure).

Mechanical prostheses offer durability and longevity. Despite the problems associated with anticoagulation and small risks of thrombosis *in situ* (usually engendered by a period of under-anticoagulation) and infective endocarditis, they remain the first choice for patients whose life expectancy significantly exceeds 10 years. Patients with significant mitral valve disease usually have another indication for anticoagulation (e.g. atrial fibrillation and/or left atrial enlargement) and mechanical prostheses are therefore most commonly used when mitral repair is not an option.

Bioprostheses avoid the need for obligatory oral anticoagulation and are most commonly used for aortic valve replacement in the elderly (70% in isolated AVR, 82% in patients undergoing AVR and coronary artery bypass graft). Valve lifespan is often quoted as 10 years, although modern stentless bioprostheses may last for considerably longer. Bioprosthetic valve degeneration occurs more slowly in the elderly and affects around 10% of patients over the age of 70 years at 15-year follow-up.

Table 116.1 Target international normalized ratio (INR) for mechanical prostheses.[3]

Prosthesis thrombogenicity[a]	Patient-related risk factors[b]	
	No risk factor	≥1 risk factor
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

[a]Prosthesis thrombogenicity: low, Carbomedics (aortic position), Medtronic Hall, St Jude Medical (without Silzone); medium, Bjork–Shiley, other bileaflet valves; high, Lillehei–Kaster, Omniscience, Starr–Edwards.
[b]Patient-related risk factors: mitral, tricuspid or pulmonary valve replacement; previous thromboembolism; atrial fibrillation; left atrial diameter >5 cm; dense left atrial spontaneous echo contrast; mitral stenosis of any degree; left ventricular ejection fraction <35%; hypercoagulable state.

Anticoagulation

Comprehensive guidelines for the prevention of thromboembolic events in VHD have been produced by the European Society of Cardiology. The indications for anticoagulation and recommended international normalized ratio (INR) for patients with prosthetic valves or native valve disease are summarized in Table 116.1. The recommended target INR for patients with mechanical prosthetic valves is 2.5–4.0, the intensity of anticoagulation varying according to the type of valve, its position and the patient's innate thrombotic risk.

The main difficulty with anticoagulation, particularly in the elderly, is the small risk of serious haemorrhage, which can be reduced by careful monitoring (with assistance from the family if necessary). Common causes of fluctuating levels are intercurrent illness, dehydration, dietary alterations (particularly excess alcohol consumption) and drug interactions – often no reason can be found. Excessive departures from the desired range (i.e. INR >7.0 or <1.5) may require hospital admission. High-dose intravenous vitamin K can complicate the reintroduction of warfarin and should be avoided unless there is evidence of active bleeding – haematological advice is recommended.

Complications

The symptoms of prosthetic valve dysfunction are often subtle and the clinician should have a low threshold for arranging further investigation or referral to a specialist centre. Prosthetic valve endocarditis is a dangerous condition and the diagnosis should be considered in any patient with a prosthetic valve who becomes unwell; symptoms of infection may be atypical or absent in the elderly. Specialist investigation and treatment are virtually always necessary.

Echocardiography is the investigation of choice for the routine follow-up of elderly patients with prosthetic valves and an integral part of the assessment of suspected malfunction. In many situations transthoracic imaging is inconclusive, particularly in patients with metallic valves, and in these circumstances a transoesophageal study should be performed.

The risk of thromboembolism in patients with prosthetic valves is ~1–3% per year. The rate is higher for mitral than aortic valves and lower in those with bioprostheses. Obstruction of a prosthetic valve is nearly always thrombotic and occurs more frequently with mechanical valves (Figure 116.16). The mortality associated with emergency presentation approaches 50% and early recognition and immediate intervention are essential. Revision surgery is the preferred treatment strategy although thrombolysis may be a preferred option in high-risk elderly patients.

Many elderly patients with bioprosthetic valves are now in their second decade following surgery. Bioprosthetic stenosis or regurgitation may eventually develop secondary to progressive calcification, degeneration and/or rupture of the valve cusps. Aortic regurgitation in this setting has been successfully treated by TAVI within the original prosthesis (the so-called 'valve-in-valve' procedure). Other mechanical complications include suture dehiscence (which may occur in the early postoperative period or as a complication of infective endocarditis), strut fracture or haemolysis.

All patients with a prosthetic valve are at risk of infective endocarditis and should receive antibiotic prophylaxis when appropriate. There is considerable variability between the various national and international bodies as to when antibiotic prophylaxis should be used, but there is agreement that patients with prosthetic valves are at higher

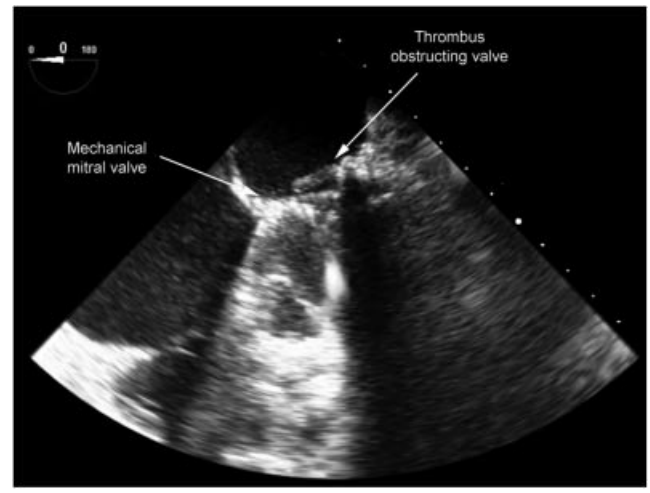


Figure 116.16 TOE demonstrating laminated thrombus (arrowed) obstructing a prosthetic mitral valve.

Table 116.2 UK and European guidelines for antibiotic prophylaxis against infective endocarditis.

	UK guidelines	European guidelines
Patients at higher risk of developing infective endocarditis	Acquired valvular heart disease with stenosis or regurgitation Valve replacement Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus and closure devices that are judged to be endothelialized Hypertrophic cardiomyopathy Previous infective endocarditis	Patients with prosthetic valves Previous infective endocarditis Congenital heart disease: Cyanotic congenital heart disease (either not repaired or repaired with a residual defect) Repaired congenital heart disease (for 6 months post-procedure) Where a residual defect persists at the site of implantation of prosthetic material or a device
Procedures requiring antibiotic prophylaxis in high-risk patients	Gastrointestinal and genitourinary procedures at a site where there is suspected pre-existing infection	*Dental:* recommended for any procedure requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa *Respiratory tract:* not recommended *GI or urogenital (including TOE)*: not recommended *Skin and soft tissue:* not recommended

risk. Current UK and European guidelines are summarized in Table 116.2.

Infective endocarditis

Introduction

In recent years, the number of elderly patients presenting with infective endocarditis has risen and staphylococcal and prosthetic valve endocarditis are increasingly prevalent in this group. Echocardiography is the principal investigative tool and the wide availability of transoesophageal imaging has greatly increased diagnostic sensitivity and specificity, in addition to providing invaluable preoperative anatomical information when cardiac surgery is necessary. These advances have been reflected by new diagnostic criteria which incorporate echocardiographic data to increase accuracy. Recent European guidelines for prompt diagnosis, specialist assessment, appropriate antibiotic therapy and timely surgery have potential for a significant impact on morbidity and mortality.

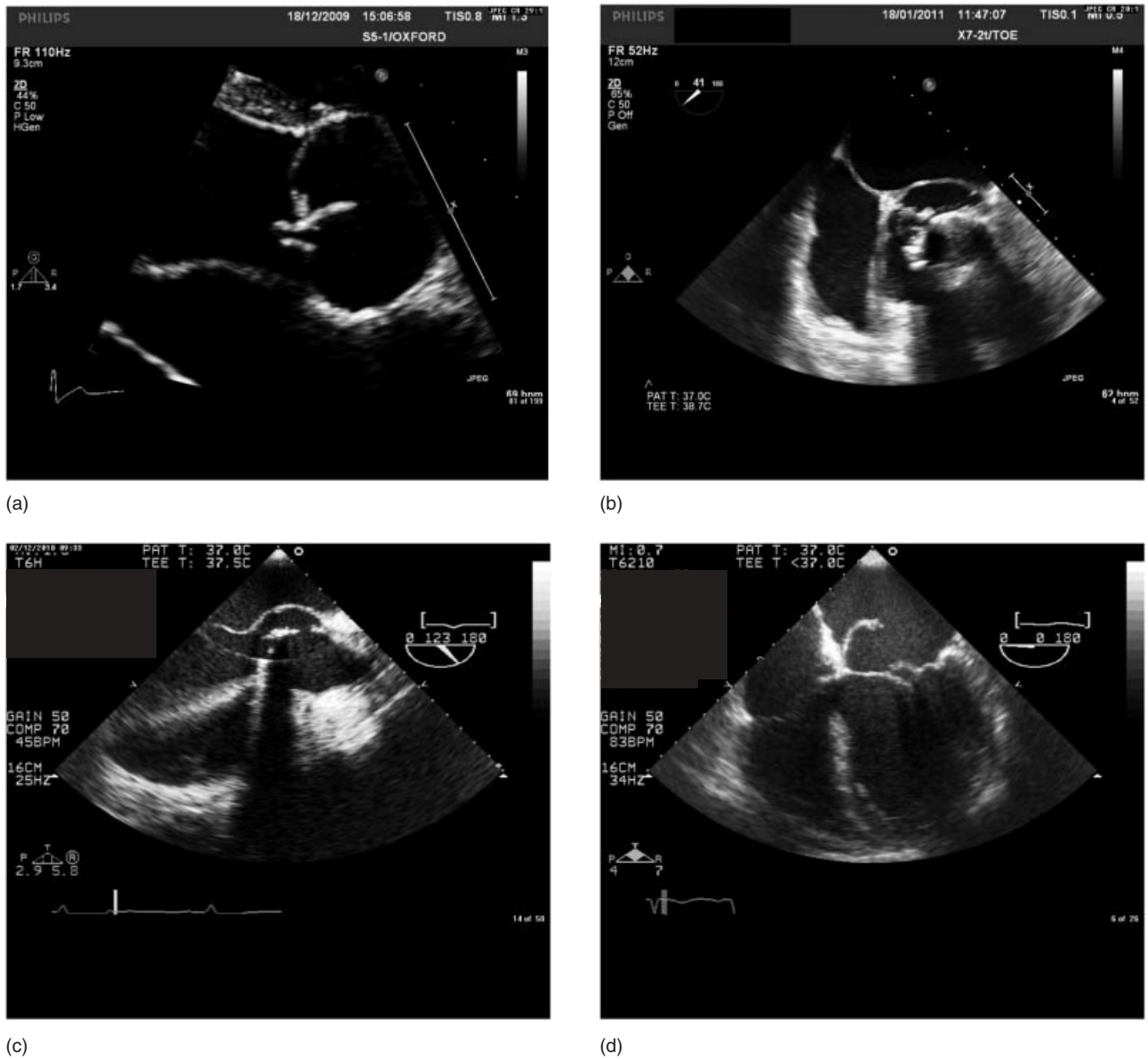
Epidemiology

The elderly form an increasing proportion of patients presenting with infective endocarditis and their mortality is higher than in younger patients. Although the absolute incidence in elderly subjects is unknown, the overall annual incidence in Western populations is approximately 2 per 100 000 population, one-third of whom are aged over 65 years. Streptococci and staphylococci are the most common causative organisms in all age groups, the latter being the predominant organism in prosthetic valve endocarditis.

Diagnosis

The classical history and typical physical signs of infective endocarditis may be absent in the elderly and diagnosis is often difficult. Therefore, a high index of suspicion is important. Patients with prosthetic valves represent a particularly high-risk group and the diagnosis of infective endocarditis should be actively sought in those who present with non-specific symptoms, prosthetic obstruction or regurgitation or systemic embolism. Minimum investigations include a full blood count, biochemical screen, inflammatory indices (erythrocyte sedimentation rate and/or C-reactive protein) and at least three sets of blood cultures from two separate sites before starting antibiotic therapy. The first two sets of blood cultures are positive in 90% of cases of infective endocarditis.

Echocardiography is invaluable, allowing the detection of vegetations, assessment of valvular incompetence and investigation of complications, such as cusp perforation or abscess formation (Figure 116.17). Vegetations appear as echogenic masses attached to valve leaflets or occasionally other intracardiac structures, although only those larger than 1–2 mm in size will be detected. Therefore, although transthoracic echocardiography should be performed, a negative study does not exclude the diagnosis. More definitive information may be obtained from a transoesophageal examination, which should be considered in all patients with proven or suspected infective endocarditis. The procedure has a high negative predictive value and is particularly sensitive in the detection of vegetations or abscesses. The old von Reyn diagnostic criteria have now been superseded by the new 'Duke' criteria, which



(a) (b)

(c) (d)

Figure 116.17 (a) Perforation of a bicuspid aortic valve secondary to infective endocarditis causing severe aortic regurgitation. (b) TOE demonstrating a large abscess cavity surrounding a prosthetic aortic valve secondary to infective endocarditis. (c) Large abscess cavity secondary to infective endocarditis with resulting prosthetic valve dehiscence. (d) TOE demonstrating a highly mobile vegetation on the anterior mitral valve leaflet prolapsing into the left atrium during ventricular systole.

include echocardiographic features and provide superior sensitivity and specificity.

Cardiac catheterization should be avoided in infective endocarditis because of the risk of dislodging vegetations or injecting friable tissues.

Treatment

Any febrile illness of doubtful or uncertain origin occurring in a patient with VHD should be considered as infective endocarditis until proven otherwise and referred to hospital urgently prior to *any* antibiotic administration. Optimal management requires close liaison between the cardiologist, cardiac surgeon and microbiologist. Antibiotic therapy should be started promptly after blood cultures have been taken and subsequent treatment is guided by the clinical and microbiological features. Indications for surgery include heart failure secondary to valvular regurgitation, abscess formation, failure to respond to medical therapy, recurrent systemic embolism and an unstable infected

prosthetic valve. Urgent surgery should not be delayed to allow an arbitrary period of preoperative antibiotic therapy.

Prosthetic valve endocarditis

The cumulative risk of infective endocarditis is 1–4% during the lifetime of a prosthesis. Antibiotic prophylaxis should be strongly considered in this group of patients, who should also receive careful education regarding the need for rigorous dental and skin hygiene – intravenous cannulae, urinary catheters and indwelling lines should be avoided whenever possible. Prosthetic valve endocarditis is a dangerous disease with a mortality of ~50% and further surgery is usually required, often as an emergency. Therefore, it should always be managed in a cardiothoracic surgical centre unless close communication can be maintained and rapid transfer is possible if needed. Transthoracic echocardiography is inadequate in this situation and prosthetic valve patients with unexplained pyrexia should be referred for transoesophageal imaging.

Conclusion

Valvular heart disease and infective endocarditis are increasingly common in the elderly population. Rheumatic heart disease is now uncommon in industrialized nations but still a major burden in the developing world. Most valvular pathology is now degenerative, particularly in those aged above 75 years. Mitral regurgitation and aortic stenosis are the most common lesions. Symptomatic VHD will continue to rise in the elderly with consequent huge implications for medical resources.

Diagnosis can be difficult and is often complicated by the presence of coincident medical conditions and the physiological effects of ageing. Transthoracic echocardiography is the investigation of choice supplemented by transoesophageal imaging when appropriate. Cardiac catheterization is only necessary if there is diagnostic doubt and for the preoperative detection of coronary artery disease if surgery is required. The risks of valve surgery are relatively low in elderly subjects provided that patients are carefully selected with optimization of their preoperative status: the risks rise significantly in the presence of left ventricular impairment, renal insufficiency and cerebrovascular or coronary artery disease. Balloon mitral valvuloplasty provides an alternative to surgery for suitable elderly patients with mitral stenosis and new percutaneous techniques of TAVI and mitral valve repair have an exciting future. Thus, although medical therapy is useful in specific situations, interventional treatment should not be denied on the grounds of age alone and early referral for expert assessment is recommended.

Key points

- The widespread availability of echocardiography has revolutionized the investigation of valvular heart disease (VHD) by providing accurate and non-invasive assessment of severity and a means of monitoring disease progression.
- In elderly patients, many of the classical manifestations of VHD may be attenuated by the effects of ageing on the cardiovascular system, namely atherosclerosis, hypertension and valve calcification.
- Progression of VHD is variable after the onset of symptoms but generally occurs over a 5–10 year period with a 20% 5 year and a 40% 10 year mortality for those treated medically.
- Echocardiography is the principal investigative tool for infective endocarditis and the wide availability of transoesophageal imaging has greatly increased diagnostic sensitivity and specificity, in addition to providing invaluable preoperative anatomical information when cardiac surgery is necessary.
- Indications for surgery for infective endocarditis include heart failure secondary to valvular regurgitation, abscess formation, failure to respond to medical therapy, recurrent systemic embolism and an unstable infected prosthetic valve.

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CHAPTER 117

Infections of the central nervous system

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Meningitis

Viral meningitis

Epidemiology and aetiology

Viruses are the major causes of the aseptic meningitis syndrome, which has been defined as any meningitis (infectious or non-infectious) for which a cause is not apparent after initial evaluation and routine stains and cultures of cerebrospinal fluid (CSF). The most common aetiological agents of the aseptic meningitis syndrome in adults are the non-polio enteroviruses (specifically Coxsackie and echoviruses), which account for 85–95% of cases in which a pathogen is identified.[1] These viruses are worldwide in distribution. In temperate climates, infections occur with a peak incidence in the summer and early autumn. Other viral causes of the aseptic meningitis syndrome include arboviruses (e.g. St Louis encephalitis virus, the California encephalitis group of viruses, West Nile virus and the agent of Colorado tick fever), mumps virus, human immunodeficiency virus (HIV) and the herpes viruses [herpes simplex viruses (HSVs) types 1 and 2 and varicella zoster virus (VZV)]. The DNA of HSV (mostly HSV type 2) has been detected in the CSF of patients with recurrent benign lymphocytic meningitis (formerly known as Mollaret's meningitis).[2]

Clinical presentation

Patients with viral meningitis often present with typical symptoms and signs of meningitis, including headache, meningismus, fever and photophobia.[1,3] Symptoms associated with the causative virus may also be present, such as vomiting and diarrhoea with the enteroviruses, vesicular rash with HSV and a mononucleosis-like syndrome with primary HIV infection. The duration of illness in enteroviral meningitis is usually less than 1 week, with many patients reporting improvement after lumbar puncture, probably as a result of a reduction in intracranial pressure.

Diagnosis

In enteroviral meningitis, lumbar puncture usually reveals a lymphocytic pleocytosis (100–1000 cells mm^{-3}), although there may be a predominance of neutrophils early in the course of infection; however, this quickly gives way to a lymphocytic predominance over the first 6–48 h.[1,3,4] CSF protein is elevated, whereas glucose may be normal or low, although these abnormalities, if present, are usually mild. Similar CSF abnormalities are usually observed in other causes of viral meningitis. Viral cultures are rarely helpful in the aetiological diagnosis of the aseptic meningitis syndrome; in one study of viral cultures on 22 394 CSF samples, virus was recovered from only 5.7% of samples, most of which were enteroviruses (98.4%).[5] Acute and convalescent serum titres may be obtained to identify specific aetiological agents but are not helpful in acute diagnosis and management.

The polymerase chain reaction (PCR) has been shown to be useful in the diagnosis of meningitis due to HSV types 1 and 2 and VZV[3] and may be helpful in the identification of HIV in the CSF or plasma of patients with meningitis following primary infection. Reverse transcription-polymerase chain reaction (RT-PCR) has also been utilized for detecting enteroviral RNA, with sensitivity ranging from 86 to 100% and specificity from 92 to 100% in the diagnosis of enteroviral meningitis.[1,3,4]

Therapy

Viral meningitis is usually a self-limited illness and in the majority of cases only supportive therapy is indicated.[1,3] Pleconaril, a novel compound that integrates into the hydrophobic pocket of picornaviruses, has been shown to have beneficial effects on the clinical, virological, laboratory and radiological parameters in patients with severe enterovirus infections. In one randomized, multi-centre, double-blind, placebo-controlled trial of 607 patients with enteroviral meningitis, pleconaril shortened the course of

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illness especially early in the disease course.[6] Pleconaril, however, has not achieved approval by the US Food and Drug Administration (FDA) because it induces CYP3A enzyme activity and has the potential for drug interactions; therefore, the sponsor has not sought approval. In cases associated with HSV infection (most often an initial infection with HSV type 2), treatment of the genital infection with antiviral therapy (e.g. acyclovir) often results in resolution of the meningitis.

Bacterial meningitis

Epidemiology and aetiology

Although numerous bacterial pathogens have been reported to cause meningitis in the elderly, certain agents are isolated more frequently.[3] *Streptococcus pneumoniae* is the most common cause of bacterial meningitis in the elderly. A contiguous (e.g. sinusitis, otitis media or mastoiditis) or distant (e.g. endocarditis or pneumonia) site of infection is often identified. More serious pneumococcal infections occur in elderly patients and in those with underlying conditions such as asplenia, multiple myeloma, alcoholism, malnutrition, diabetes mellitus and hepatic or renal disease. *S. pneumoniae* is also the most common aetiological agent of meningitis in patients with basilar skull fracture and CSF leak. In the USA, the overall mortality rates for pneumococcal meningitis have ranged from 19 to 26%. In one study of 352 episodes of community-acquired pneumococcal meningitis in adults, 70% of cases were associated with an underlying disorder and the overall in-hospital mortality rate was 30%;[7] in patients aged 60 years or older, death was more likely secondary to systemic complications. For this reason, the 23-valent pneumococcal vaccine is recommended for all patients over the age of 64 years and for those in groups at high risk for serious pneumococcal infection.

Persons at risk for infection (including meningitis) with *Listeria monocytogenes* are the elderly (≥50 years of age), those with underlying malignancy, alcoholics, those receiving corticosteroids, immunosuppressed adults (e.g. transplant recipients) and patients with diabetes mellitus and iron overload disorders.[3] Cases have also been reported in patients receiving treatment with anti-tumour necrosis factor alpha agents. Although *L. monocytogenes* is an unusual cause of bacterial meningitis in the USA, it is associated with high mortality rates (15–29%). Outbreaks of *Listeria* infection have been associated with the consumption of contaminated coleslaw, raw vegetables and milk, with sporadic cases traced to contaminated cheese, turkey franks, alfalfa tablets and processed meats; this points to the intestinal tract as the usual portal of entry. However, the incidence has been decreasing, likely as a result of a decrease in the prevalence of *Listeria* in ready-to-eat foods.

Bacterial meningitis caused by aerobic Gram-negative bacilli (e.g. *Klebsiella* species, *Escherichia coli, Serratia marcescens, Salmonella* and *Pseudomonas aeruginosa*) is found in the elderly, occurring after head trauma or neurosurgical procedures and in patients with Gram-negative bacteraemia.[3,8] Some cases have been associated with disseminated strongyloidiasis in the hyperinfection syndrome, in which meningitis caused by enteric bacteria occurs secondary to seeding of the meninges during persistent or recurrent bacteraemias associated with migration of infective larvae; alternatively, the larvae may carry enteric organisms on their surfaces or within their own gastrointestinal tracts as they exit the intestine and subsequently invade the meninges.

Other bacterial species are less common causes of bacterial meningitis in the elderly.[3] *Neisseria meningitidis* may cause meningitis during epidemics (caused by serogroups A and C) or in sporadic outbreaks (serogroup B), although meningitis caused by this microorganism is more common in children and adults. There is an increased incidence of neisserial infections, including that caused by *N. meningitidis*, in persons with deficiencies of the terminal complement components (C5, C6, C7, C8 and perhaps C9), although the case fatality rates in these patients are lower than in those with an intact complement system. *Hemophilus influenzae* meningitis in elderly adults is associated with concurrent infections such as sinusitis, otitis media and pneumonia and underlying conditions such as chronic obstructive pulmonary disease, asplenia, diabetes mellitus, immunosuppression and head trauma with CSF leak. Meningitis caused by *Staphylococcus aureus* is usually found in the early postneurosurgical period or after head trauma or in patients with CSF shunts; other underlying conditions include diabetes mellitus, alcoholism, chronic renal failure requiring haemodialysis, injection drug use and malignancies. *Staphylococcus epidermidis* is the most common cause of meningitis in patients with CSF shunts. The group B streptococcus (*Streptococcus agalactiae*) may cause meningitis in adults; risk factors include age greater than 60 years, diabetes mellitus, cardiac disease, collagen vascular disorders, malignancy, alcoholism, hepatic failure, renal failure, previous stroke, neurogenic bladder, decubitus ulcers and corticosteroid therapy.

Clinical presentation

The classic symptoms and signs in patients with bacterial meningitis include headache, fever and meningismus; these are seen in more than 85% of patients.[3] In a review of community-acquired meningitis in adults, the classic triad of fever, nuchal rigidity and change in mental status was found in only two-thirds of patients. Other findings include cranial nerve palsies (~10–20%), seizures (~30%) and Kernig's and/or Brudzinski's signs. However, in a

prospective study that examined the diagnostic accuracy of meningeal signs in adults with suspected meningitis, the sensitivity of Kernig's sign was 5%, Brudzinski's sign 5% and nuchal rigidity 30%, indicating that the presence of these signs did not accurately distinguish patients with meningitis from those without meningitis. In another review of 696 episodes of community-acquired bacterial meningitis, the triad of fever, neck stiffness and altered mental status was found in only 44% of patients,[9] although 95% presented with at least two of four symptoms (fever, headache, stiff neck, altered mental status).

However, elderly patients with bacterial meningitis, especially those with underlying conditions (e.g. diabetes mellitus or cardiopulmonary disease), may present insidiously with lethargy, confusion, anorexia, no fever and variable signs of meningeal inflammation.[3] In one review, confusion was very common in elderly patients on initial examination and occurred in 92 and 78% of those with pneumococcal and Gram-negative bacillary meningitis, respectively. There may be a history of an antecedent or concurrent illness such as sinusitis, otitis media or pneumonia. In the elderly patient, an altered or changed mental status should not be ascribed to other causes until bacterial meningitis has been excluded by CSF examination.

Diagnosis

The diagnosis of bacterial meningitis rests with CSF examination following lumbar puncture.[3] CSF characteristics of bacterial meningitis include an elevated opening pressure in virtually all patients. The white blood cell count is elevated in untreated bacterial meningitis (usually 1000–5000 cells mm^{-3}) with a neutrophilic predominance, although lymphocytes may predominate in *L. monocytogenes* meningitis (~30% of cases). Elevated protein (100–500 mg dl^{-1}) and decreased glucose (<40 mg dl^{-1}) levels are also typically observed; a CSF: serum glucose level of ≤ 0.4 mg dl^{-1} is found in the majority of patients with acute bacterial meningitis.

The CSF Gram stain provides rapid and accurate identification of the causative organism in 60–90% of patients with bacterial meningitis, with a specificity of almost 100%. Bacteria are observed in 90% of cases of meningitis caused by *S. pneumoniae*, but in only about one-third of patients with *L. monocytogenes* meningitis.[3] CSF cultures are positive in 70–85% of patients overall. The probability of identifying the organism in CSF cultures may decrease in patients who have received prior antimicrobial therapy.

Several rapid diagnostic tests are available to aid in the aetiological diagnosis of bacterial meningitis.[3] Latex agglutination tests detect the antigens of *H. influenzae* type b, *S. pneumoniae, N. meningitidis, E. coli* K1 and *S. agalactiae*. The overall sensitivity ranges from 50 to 100% (somewhat lower for *N. meningitidis* because of the limited immunogenicity of the group B meningococcal polysaccharide), although these tests are highly specific. However, the routine use of latex agglutination for the aetiological diagnosis of bacterial meningitis has recently been questioned and is no longer routinely recommended, because the results do not appear to modify the decision to administer appropriate antimicrobial therapy and false-positive tests have been reported.[10] Latex agglutination may be most useful for the patient who has been pretreated with antimicrobial therapy and whose CSF Gram stain and cultures are negative, although it must be emphasized that a negative test does not rule out infection by a specific meningeal pathogen. An immunochromatographic test for the detection of *S. pneumoniae* in CSF has been found to have an overall sensitivity of 95–100% in the diagnosis of pneumococcal meningitis,[11] but more studies are needed to assess the usefulness of this test.

Nucleic acid amplification tests (e.g. PCR) have been used to amplify DNA from patients with bacterial meningitis caused by several pathogens. In one study, broad-based PCR demonstrated a sensitivity of 100%, a specificity of 98.2%, a positive predictive value of 98.2% and a negative predictive value of 100%.[3] The sensitivity and specificity of PCR in CSF for the diagnosis of pneumococcal meningitis are 92–100% and 100%, respectively.[11] There are some problems with false-positive results, but further refinements in PCR may demonstrate its usefulness in the diagnosis of bacterial meningitis in patients who have already received antibiotics and when the CSF Gram stain, bacterial antigen tests and cultures are negative.

Antimicrobial therapy

In patients suspected of having bacterial meningitis, blood cultures should be obtained and a lumbar puncture done immediately. If purulent meningitis is present, targeted antimicrobial therapy should be initiated on the basis of results of Gram staining (i.e. vancomycin and a third-generation cephalosporin if Gram-positive diplococci are seen). However, if no aetiological agent can be identified or if there is a delay in the performance of the lumbar puncture, empirical antimicrobial therapy should be initiated on the basis of the patient's age and the underlying disease status.[3,10] In patients who are immunosuppressed and have a history of central nervous system (CNS) disease, focal neurological deficits or seizures or if papilloedema is found on funduscopic examination, a computed tomographic (CT) scan is recommended prior to lumbar puncture, with empirical antimicrobial therapy initiated before scanning. Empirical therapy for elderly patients with suspected community-acquired bacterial meningitis should include vancomycin, ampicillin and a third-generation cephalosporin (see the following text for specific recommendations). Once the meningeal pathogen

has been identified, antimicrobial therapy can be modified for optimal treatment (Table 117.1); recommended dosages for CNS infections are shown in Table 117.2.

For the treatment of bacterial meningitis in elderly persons, choices of antimicrobial therapy should be based on prevalent trends in antimicrobial susceptibility. For meningitis caused by *S. pneumoniae*, therapy in recent years has been significantly altered by changes in pneumococcal susceptibility patterns.[3,10] Numerous reports from around the world have documented strains of pneumococci that are of intermediate susceptibility [minimal inhibitory concentration (MIC) range 0.1–1.0 $\mu g\,ml^{-1}$] and highly (MIC $\geq$2.0 $\mu g\,ml^{-1}$) resistant to penicillin G; susceptible strains have MICs $\leq$ 0.06 $\mu g\,ml^{-1}$. On the basis of these trends and because achievable CSF concentrations of penicillin are inadequate to treat these resistant isolates, penicillin can never be recommended as empirical therapy for patients with suspected or proven pneumococcal meningitis, pending results of susceptibility testing. As an empirical regimen, we recommend the combination of vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone). If the isolate is susceptible to penicillin, high-dose intravenous penicillin G or ampicillin is adequate. If the isolate is of intermediate susceptibility to penicillin, only the third-generation cephalosporin need be continued. However, if the pneumococcal isolate is highly resistant to penicillin, the combination of vancomycin and the third-generation cephalosporin should be continued, because vancomycin therapy alone may not be optimal therapy for patients with pneumococcal meningitis. Any patient who is not improving as expected or has a pneumococcal isolate for which the cefotaxime/ceftriaxone MIC is $\geq$ 2.0 $\mu g\,ml^{-1}$ should undergo a repeat lumbar puncture to document sterility of CSF after 36–48 h of therapy;[10] this may be especially important for patients who are also receiving adjunctive dexamethasone therapy (see the following text). Some experts have also recommended the addition of rifampin for these highly resistant strains, although clinical data are lacking. In patients not responding, administration of vancomycin by the intraventricular or intrathecal route is a reasonable adjunct. Newer fluoroquinolones (e.g. moxifloxacin) that have *in vitro* activity against *S. pneumoniae* may have utility in the treatment of pneumococcal meningitis;[3,10] the newer fluoroquinolones (specifically moxifloxacin), combined with either a third-generation cephalosporin or vancomycin, may emerge as an option in the treatment of bacterial meningitis.

Adjunctive therapy

Despite the availability of effective antimicrobial therapy, the mortality and morbidity from bacterial meningitis have not changed significantly over the past 30 years. A major factor contributing to increased morbidity and mortality is the generation of a subarachnoid space inflammatory response following antimicrobial-induced bacterial lysis;[3] therefore, several clinical trials were performed to examine the effectiveness of adjunctive dexamethasone in attenuating this inflammatory response in patients with bacterial meningitis. Most of these studies were conducted in infants and children with predominantly *H. influenzae* type b meningitis and supported the routine use of adjunctive dexamethasone in this patient population.[3,10] In a prospective, randomized, double-blind trial in 301 adults with bacterial meningitis, adjunctive dexamethasone was associated with a reduction in the proportion of patients who had unfavourable outcomes and in the proportion of patients who died; the benefits were most striking in the subgroup of patients with pneumococcal meningitis and in those with moderate-to severe disease as assessed by the admission Glasgow Coma Scale score. Despite these results, the use of adjunctive dexamethasone in the treatment of bacterial meningitis in the developing world has been more controversial. In one randomized, double-blind, placebo-controlled trial in adolescents and adults in Vietnam with confirmed bacterial meningitis (most often caused by *Streptococcus suis*), adjunctive dexamethasone was associated with reduction in the risk of death or disability.[12] In contrast, in another randomized, double-blind, placebo-controlled trial in Malawi, there were no significant differences in mortality;[13] however, in this trial, almost 90% of patients were infected with HIV and most had advanced disease. These data suggest that adjunctive dexamethasone is not beneficial in patients in resource-poor countries when a substantial number of patients are infected with HIV.

On the basis of these data and the apparent absence of serious adverse outcomes in the patients who received dexamethasone, the routine use of adjunctive dexamethasone (0.15 $mg\,kg^{-1}$ every 6 h for 4 days, given concomitantly with or just prior to the first dose of an antimicrobial agent for maximum attenuation of the subarachnoid space inflammatory response) is warranted in adults with suspected or proven pneumococcal meningitis.[10] Adjunctive dexamethasone should not be used in patients who have already received antimicrobial therapy; if the meningitis is subsequently found not to be caused by *S. pneumoniae*, dexamethasone should be discontinued, although some experts recommend the use of adjunctive dexamethasone regardless of the microbial aetiology. However, the use of adjunctive dexamethasone is of particular concern in patients with pneumococcal meningitis caused by highly penicillin-resistant strains, since a diminished inflammatory response may significantly impair CSF vancomycin penetration. In an experimental model of *S. pneumoniae* meningitis in rabbits, the concurrent use of dexamethasone with vancomycin decreased the penetration of vancomycin into the CSF and also decreased the rate of bactericidal activity of vancomycin. However, appropriate CSF concentrations of vancomycin may be achieved when

Table 117.1 Specific antimicrobial therapy for meningitis.

Microorganism	Standard therapy	Alternative therapies
Bacteria		
Streptococcus pneumoniae		
Penicillin MIC $<0.1\,\mu g\,ml^{-1}$	Penicillin G or ampicillin	Third-generation cephalosporin[a]; vancomycin
Penicillin MIC $0.1–1.0\,\mu g\,ml^{-1}$	Third-generation cephalosporin[a]	Meropenem; vancomycin
Penicillin MIC $\geq 2.0\,\mu g\,ml^{-1}$	Vancomycin plus a third-generation cephalosporin[a,b]	Third-generation cephalosporin[a] + moxifloxacin
Enterobacteriaceae	Third-generation cephalosporin[a]	Aztreonam; fluoroquinolone; trimethoprim–sulfamethoxazole; meropenem
Pseudomonas aeruginosa	Ceftazidime[c] or cefepime[c]	Aztreonam[c]; fluoroquinolone[c]; meropenem[c]
Listeria monocytogenes	Ampicillin[c] or penicillin G[c]	Trimethoprim–sulfamethoxazole
Hemophilus influenzae		
β-Lactamase-negative	Ampicillin	Third-generation cephalosporin[a]; cefepime; chloramphenicol; aztreonam
β- Lactamase-positive	Third-generation cephalosporin[a]	Cefepime, chloramphenicol; aztreonam; fluoroquinolone
Neisseria meningitidis		
Penicillin MIC $<0.1\,\mu g\,ml^{-1}$	Penicillin G or ampicillin	Third-generation cephalosporin[a]; chloramphenicol; fluoroquinolone
Penicillin MIC $0.1–1.0\,\mu g\,ml^{-1}$	Third-generation cephalosporin[a]	Chloramphenicol; fluoroquinolone; meropenem
Streptococcus agalactiae	Ampicillin[c] or penicillin G[c]	Third-generation cephalosporin[a]; vancomycin
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin; meropenem; linezolid; daptomycin
Methicillin-resistant	Vancomycin	Trimethoprim–sulfamethoxazole; linezolid; daptomycin
Staphylococcus epidermidis	Vancomycin[b]	Linezolid
Myobacteria		
Mycobacterium tuberculosis	Isoniazid + rifampin + pyrazinamide + ethambutol	Ethionamide; streptomycin; fluoroquinolone
Spirochetes		
Treponema pallidum	Penicillin G	Doxycycline[d]; ceftriaxone[d]
Borrelia burgdorferi	Third-generation cephalosporin[a]	Penicillin; doxycycline
Fungi		
Cryptococcus neoformans	Amphotericin B deoxycholate[f] + 5-flucytosine	Fluconazole
Candida species	Amphotericin B deoxycholate ± 5-flucytosine	Fluconazole[d]
Coccidioides immitis	Fluconazole	Amphotericin B[e]; itraconazole; voriconazole

[a] Cefotaxime or ceftriaxone.
[b] Addition of rifampin should be considered; see text for details.
[c] Addition of an aminoglycoside should be considered.
[d] The value of these antimicrobial agents has not been established.
[e] Intravenous and intraventricular administration.
[f] See text for indications of utilizing a lipid formulation of amphotericin B.

Table 117.2 Recommended dosages of selected antimicrobial agents for central nervous system infections in adults with normal renal and hepatic function.

Antimicrobial agent	Total daily dose	Dosing interval (h)
Acyclovir	30 mg kg^{-1}	8
Amikacin[a]	15 mg kg^{-1} ←	8
Amphotericin B deoxycholate[b]	0.6–1.0 mg kg^{-1}	24
Amphotericin B lipid formulation	5 mg kg^{-1}	24
Ampicillin	12 g	4
Aztreonam	6–8 g	6–8
Cefepime	6 g	8
Cefotaxime	8–12 g	4–6
Ceftazidime	6 g	8
Ceftriaxone	4 g	12–24
Chloramphenicol[c]	4–6 g	6
Ciprofloxacin	800–1200 mg	8–12
Fluconazole	400–800 mg	24
Flucytosine[d,e]	100 mg kg^{-1}	6
Gentamicin[a]	5 mg kg^{-1}	8
Imipenem	2 g	6
Liposomal amphotericin B (AmBisome)	5 mg kg^{-1}	24
Meropenem	6 g	8
Metronidazole	30 mg kg^{-1}	6
Nafcillin	9–12 g	4
Oxacillin	9–12 g	4
Penicillin G	24 million units	4
Rifampicin (rifampin)	600 mg	24
Tobramycin[a]	5 mg kg^{-1}	8
Trimethoprim–sulfamethoxazole[f]	10–20 mg kg^{-1}	6–12
Vancomycin[g]	30–60 mg kg^{-1}	8–12
Voriconazole[h]	8 mg kg^{-1}	12

[a] Need to monitor peak and trough serum concentrations.
[b] Can increase dosage to 1.5 mg kg^{-1} per day in severely ill patients.
[c] Higher dose recommended for pneumococcal meningitis.
[d] Oral administration.
[e] Maintain serum concentrations from 50 to 100 μg ml^{-1}.
[f] Dosage based on trimethoprim component.
[g] May need to monitor cerebrospinal fluid concentrations in severely ill patients.
[h] Load with 6 mg kg^{-1} i.v. every 12 h for two doses.

patients are receiving adequate dosing of vancomycin; in one study of 14 patients with pneumococcal meningitis, administration of vancomycin at a continuous infusion of 60 mg kg^{-1} per day, after a 15 mg kg^{-1} loading dose, led to a mean CSF concentration of 7.2 μg ml^{-1}.[14] In patients with pneumococcal meningitis caused by strains that are highly resistant to penicillin or cephalosporins, careful observation and follow-up are critical to determine whether the use of adjunctive dexamethasone is associated with adverse clinical outcome in these patients.

Tuberculous meningitis

Epidemiology and aetiology

Almost all cases of tuberculous meningitis are caused by *Mycobacterium tuberculosis*. Risk factors for the development of tuberculous meningitis include a history of prior tuberculous disease, advanced age, homelessness, alcoholism, gastrectomy, diabetes mellitus and immunosuppression.[15] HIV infection has influenced the epidemiology of tuberculosis, in which extrapulmonary disease occurs in more than 70% of patients with AIDS, but in only 24–45% of patients with tuberculosis and less advanced HIV infection.

Clinical presentation

Tuberculous meningitis often has a subacute, indolent presentation with a prodrome characterized by malaise, low-grade fever, headache and personality changes;[15,16] this is followed by a meningitic phase with worsening headache, meningismus, nausea, vomiting and waxing-and-waning mental status. A history of prior clinical tuberculosis is obtained in fewer than 20% of cases. Up to 30% of patients have focal neurological signs on presentation, usually consisting of unilateral or, less commonly, bilateral cranial nerve palsies [cranial nerve (CN) VI is the most frequently affected]. Hemiparesis may result from ischaemic infarction, most commonly in the distribution of the territory of the middle cerebral artery. In one study of 122 patients with tuberculous meningitis, stroke was found in 45% and manifested anywhere from the time of initial presentation to months after the start of therapy.[17]

Diagnosis

CSF examination in patients with tuberculous meningitis often reveals a lymphocytic pleocytosis (5–500 cells mm^{-3}), although early in the course of disease there may be a mix of both lymphocytes and neutrophils.[15,16] Following treatment with antituberculous drugs, a so called 'therapeutic paradox' may develop with a change in the white blood cell differential from a lymphocytic to a neutrophilic predominance. There is usually an elevated CSF protein (median of 150–200 mg dl^{-1}) and often a very low glucose (<20 mg dl^{-1}, although the median value is 40 mg dl^{-1}). Because of the small number of organisms present in the CSF, acid-fast bacilli (AFB) smears are often negative (fewer than 25% of smears are positive).

On the basis of these poor results, several rapid diagnostic tests are under development to aid in the diagnosis of tuberculous meningitis. Although PCR testing, which can detect *M. tuberculosis* DNA in CSF specimens, is promising; the lack of standardization makes interpretation difficult[16,18]

and older assays had varying sensitivities (33–90%) and specificities (80–100%). Newer PCR assays have improved sensitivity for the diagnosis of tuberculous meningitis. Although largely experimental, detection of specific CSF antigens and antibodies is another way in which tuberculous meningitis may be diagnosed.

CT and magnetic resonance (MR) scanning may be useful to support the diagnosis of tuberculous meningitis.[15,16] Hydrocephalus is frequently present at diagnosis or develops during the course of infection. The presence of basal cistern enhancement is also supportive evidence for the diagnosis. MR may be superior to CT in the identification of basilar meningeal inflammation and small tuberculoma formation.

Antimicrobial therapy

Therapy for tuberculous meningitis is often initiated on the basis of the patient's clinical presentation, as cultures may take weeks to become positive and may remain negative in up to 20% of patients. Therapy with isoniazid, rifampin, ethambutol and pyrazinamide for 2 months, followed by isoniazid and rifampin for 7–10 months, should be adequate for patients with drug-sensitive tuberculous meningitis.[16,18] In HIV-infected patients, therapy is continued for at least 12 months. However, therapy for tuberculous meningitis may need to be individualized, with longer durations in patients with a higher severity of illness. For patients with suspected tuberculous meningitis caused by multidrug-resistant strains, at least five drugs should be used pending susceptibility testing. The fluoroquinolones (e.g. moxifloxacin) penetrate well into CSF and have good *in vitro* activity against *M. tuberculosis*. Most authorities recommend continuing therapy for a total of 18–24 months in patients with multidrug-resistant tuberculous meningitis.

Adjunctive Therapy

Corticosteroids have been shown to be of value as adjunctive therapy in tuberculous meningitis with resolution of fevers, improved mental status and, most importantly, the ability to treat or avert the development of spinal block.[15,16,18] Despite some controversy, most authorities recommend the use of corticosteroids in patients with tuberculous meningitis. Recommended therapy is prednisone $1\,mg\,kg^{-1}$ per day slowly tapered over 1 month, although varying doses of dexamethasone or hydrocortisone have also been used. In a randomized, double-blind, placebo-controlled trial in Vietnam in patients with tuberculous meningitis, adjunctive dexamethasone improved survival in patients over 14 years of age,[19] although it probably did not prevent severe disability. A systematic review of published studies has noted a decreased risk of death or disabling residual neurological deficits in patients with tuberculous meningitis who received adjunctive dexamethasone therapy.[20]

Spirochetal meningitis

Epidemiology and aetiology

Treponema pallidum (the aetiological agent of syphilis) disseminates to the CNS early during infection, with CSF abnormalities detected in 5–9% of patients with seronegative primary syphilis.[21] The overall incidence of neurosyphilis has increased in association with HIV infection; in one report, 44% of all patients with neurosyphilis had AIDS and 1.5% of AIDS patients were found to have neurosyphilis at some point during the course of their illness.

Approximately 10–15% of patients with Lyme disease will develop signs and symptoms of meningitis, usually early in the course of infection.[22] Infection with *Borrelia burgdorferi* should be suspected in a patient with meningitis in association with other symptoms of Lyme disease, such as erythema migrans, malaise, myalgias and arthralgias. Meningitis usually follows erythema migrans by 2–10 weeks, although only about 40% (range 10–90%) of cases of Lyme meningitis are preceded by this characteristic rash.

Clinical presentation

There are four categories of CNS involvement with *T. pallidum*.[21] Syphilitic meningitis occurs within the first 2 years of infection, with symptoms of headache, nausea, vomiting and less frequently fevers, meningismus and mental status changes. Meningovascular syphilis (found in 10–12% of individuals with CNS involvement), occurring months to years after infection, results in focal neurological findings as a result of focal syphilitic arteritis, which almost always occurs in association with meningeal inflammation; focal deficits may progress to a stroke syndrome with attendant irreversible neurological deficits. Parenchymatous neurosyphilis (10–20 years after infection) manifests as general paresis and tabes dorsalis. Gummatous disease is very rare and generally occurs more than 30 years following initial infection. Coinfection with HIV may alter the clinical course of syphilis, in which patients may be more likely to progress to neurosyphilis and show accelerated disease courses.

Symptoms of CNS infection with *B. burgdorferi* include headache, fever, meningismus, nausea and vomiting.[22] Up to 50% of patients will develop cranial nerve palsies, most commonly involving CN VII; facial nerve palsy is bilateral in 30–70% of patients, although the two sides are affected asynchronously in most cases. In untreated patients the duration of symptoms is 1–9 months and patients typically experience recurrent attacks of meningeal symptoms lasting several weeks, alternating with similar periods of milder symptoms. About half of the patients with Lyme meningitis have mild cerebral symptoms, consisting of somnolence, emotional lability, depression, impaired memory and concentration and behavioural symptoms.

Diagnosis

CSF findings in patients with CNS syphilis are non-specific, revealing a mononuclear pleocytosis (>10 cells mm^{-3} in most patients), elevated protein and a normal or slightly decreased glucose.[21] A reactive VDRL (venereal disease research laboratory) slide test in the CSF has a sensitivity of only 30–70% for the diagnosis of neurosyphilis (although the specificity is high). The treatment for neurosyphilis is indicated in the presence of any of the above abnormalities in association with the appropriate clinical setting. The fluorescent treponemal antibody absorption test (FTA-ABS) in the CSF has been examined as a possible diagnostic test for neurosyphilis; a non-reactive test effectively rules out the likelihood of neurosyphilis, although a positive test may result from leakage of small amounts of antibody absorption from the serum into CSF, making it less specific than the CSF VDRL.

The best currently available laboratory test for the diagnosis of Lyme disease is the demonstration of specific serum antibody to *B. burgdorferi*, in which a positive test in a patient with a compatible neurological abnormality is strong evidence for the diagnosis.[22] It is currently recommended that when the pretest probability of Lyme disease is 0.20–0.80, sequential testing with enzyme-linked immunosorbent assay (ELISA) and Western blot is the most accurate method for ruling in or out the possibility of Lyme disease. The sensitivity and specificity of two-tier testing in one study of patients with later manifestations of Lyme disease were 100% and 99%, respectively.[23] A lymphocytic pleocytosis (usually <500 cells mm^{-3}) is observed in the CSF, along with elevated protein and normal glucose in patients with Lyme meningitis. Antibodies and antigens to *B. burgdorferi* may be detected in the CSF by ELISA or Western blot, respectively, although antibody tests are not standardized with marked variability between laboratories. One study of 123 patients with anti-*Borrelia* antibody in CSF found that determination of the antibody index had a sensitivity of 75% and a specificity of 97% for diagnosis, although another aetiology was responsible for symptoms in 60% of patients.[24] PCR may be a useful tool for the detection of *B. burgdorferi* DNA in CSF, although PCR must still be considered experimental in the diagnosis of CNS Lyme disease.

Antimicrobial therapy

Treatment for neurosyphilis is intravenous penicillin G 18–24 million units per day in divided doses every 4 h for 10–14 days.[21] No large studies have been performed to evaluate alternative antimicrobial agents for the therapy of neurosyphilis; the tetracyclines, chloramphenicol and ceftriaxone may have potential clinical utility based on case reports, clinical experience and extrapolations from experimental animal studies. Although follow-up lumbar puncture every 6 months until the CSF changes have normalized is recommended, one recent study demonstrated that in most patients treated for neurosyphilis, normalization of the serum RPR (rapid plasma reagin) correctly predicted the success of therapy and normalization of CSF parameters after treatment.[25]

Treatment of Lyme meningitis is intravenous ceftriaxone 2 g per day for 14 days (range 10–28 days);[26] the literature contains no agreement on the duration of therapy or on the minimum adequate dose of the antimicrobial. At present, there is no evidence to support treatment durations longer than 4 weeks.

Fungal meningitis

Epidemiology and aetiology

Cryptococcus neoformans is the most common fungal cause of clinically recognized meningitis, with most cases seen in immunocompromised patients, including those with AIDS, transplant recipients and those receiving chronic corticosteroids.[27] Other underlying conditions with an increased risk for cryptococcal disease include sarcoidosis, collagen vascular disorders (e.g. systemic lupus erythematosus), chronic renal and hepatic failure and diabetes mellitus; *C. neoformans* meningitis has also been documented in apparently healthy individuals.

Meningitis due to *Candida* species is relatively rare and is often associated with disseminated disease. Risk factors include malignancy, neutropenia, chronic granulomatous disease, the presence of central venous catheters, diabetes mellitus, hyperalimentation and corticosteroid therapy.[27]

Coccidioides immitis is a fungus endemic to the semi-arid regions and the desert areas of southwestern USA. Extrapulmonary disease develops in 1–5% of symptomatic patients, although, of those, one-third to one-half have meningeal involvement. Dissemination is associated with extremes of age, male gender, non-white race and immunosuppression (e.g. corticosteroid therapy, organ transplantation, HIV infection and treatment with inhibitors of tumour necrosis factor alpha).[27–29]

Clinical presentation

Clinical presentation of cryptococcal meningitis can vary. Most patients present with signs and symptoms of subacute meningitis or meningoencephalitis, such as headache, fever, cranial nerve palsies, lethargy, coma or memory loss over several weeks.[27] HIV-infected patients with cryptococcal meningitis exhibit few differences at presentation from those without HIV. However, several clinical aspects may be more prominent in patients with AIDS given that the burden of yeast in this population is generally higher. However, AIDS patients may present with very minimal symptoms in which the only clinical findings may be fever, headache and lethargy; cranial nerve palsies are often absent. Ocular

abnormalities (e.g. cranial nerve palsies and papilloedema) occur in about 45% of patients.

Patients with *Candida* meningitis may present either abruptly or insidiously.[27] Symptoms include fever, headache and meningismus; patients may also have depressed mental status, confusion, cranial nerve palsies and focal neurological signs. The presentation is often similar to that observed with bacterial meningitis.

Meningeal infection with *C. immitis* most often follows a subacute or chronic course.[27–29] Previously healthy people with meningitis may present with the indolent onset of headache that is present for weeks or months at time of diagnosis. The patient may recall the initial infection as a period of fever and cough occurring 2–4 weeks following exposure. Other symptoms include nausea, photophobia, neck pain and stiffness, confusion, declines in cognition or memory, emotional lability and hearing or visual changes. Immunosuppressed patients, including those with AIDS, are more likely to present with a systemic illness, including fever, headache, profound malaise and lesions in the bone or skin.

Diagnosis

In most non-AIDS patients with cryptococcal meningitis, examination of the CSF reveals an elevated opening pressure, lymphocytic pleocytosis (range 20–500 cells mm^{-3}), elevated protein and normal or decreased glucose.[27] AIDS patients with cryptococcal meningitis may have very low or even normal CSF white blood cell counts; 65% of patients have fewer than 5 cells mm^{-3} in CSF. India ink examination is positive in up to 50–75% of patients with cryptococcal meningitis and the rate of positivity is even higher (~88%) in AIDS patients. As the India ink examination is difficult to perform and rates of positivity are dependent upon the experience of the laboratory, the latex agglutination test for cryptococcal polysaccharide antigen in the CSF should be performed and is both sensitive and specific for the diagnosis of cryptococcal meningitis. A presumptive diagnosis is indicated by a titre of $\geq$1:8. The presence of cryptococcal antigen in the serum is also supportive evidence for the diagnosis and may be detected in severely immunocompromised patients (i.e. those with AIDS); however, the value of the serum cryptococcal polysaccharide antigen for screening patients suspected of having meningeal disease has not been established. Routine fungal cultures of the CSF are often positive.

Examination of the CSF in patients with *Candida* meningitis typically shows a mixture of neutrophils and lymphocytes, elevated protein and decreased glucose. Yeast cells are seen on smear in ~40% of patients, with fungal cultures positive in most cases.

CSF examination in coccidioidal meningitis reveals a pleocytosis, occasionally showing a prominent eosinophilia.[27–29] Unfortunately, only about 15% of patients have positive CSF cultures. Enzyme immunoassay and immunodiffusion methods are commonly used for the detection of both IgM and IgG antibody groups; although positive serological results are helpful in diagnosis, negative results cannot be used to rule out disease. Elevated serum concentrations of complement-fixing antibodies (titres in excess of 1:32–1:64) suggest dissemination. CSF complement-fixing antibodies are present in at least 70% of patients with early meningitis and from virtually all patients as disease progresses, although antibodies may fail to develop in the serum or CSF of patients with immunodeficiencies. When present, the antibody titres appear to parallel the course of meningeal disease.

Antimicrobial therapy

The treatment for cryptococcal meningitis in non-AIDS patients is amphotericin B deoxycholate with 5-flucytosine for at least 4 weeks of induction therapy;[30] the 4 week combination regimen can be used in the subset of patients who, at presentation, have no neurological complications and CSF yeast culture results that are negative after 2 weeks of treatment. In patients experiencing toxicity to amphotericin B deoxycholate, a lipid formulation of amphotericin B may be substituted in the second 2 weeks. In patients with neurological complications, consideration should be given to extending induction therapy for a total of 6 weeks and a lipid formulation of amphotericin B can be given for the last 4 weeks. This is followed by consolidation therapy with fluconazole for 8 weeks and then maintenance therapy of 200 mg daily for 6–12 months.

In AIDS patients with cryptococcal meningitis, amphotericin B deoxycholate with 5-flucytosine for at least 2 weeks of induction therapy is recommended, followed by fluconazole consolidation therapy for a minimum period of 8 weeks.[30] A lipid formulation of amphotericin B can be substituted for amphotericin B deoxycholate among patients with or predisposed to renal dysfunction. Chronic suppressive therapy with fluconazole (200 mg daily) is then continued indefinitely in patients with AIDS to prevent relapse, although discontinuation of suppressive therapy can be considered in patients on antiretroviral therapy with CD4 cell counts $>100\,mm^{-3}$ and an undetectable or very low HIV RNA level sustained for $\geq$3 months (minimum of 12 months of antifungal therapy).

Treatment for meningitis caused by *Candida* species is amphotericin B, with or without 5-flucytosine.[27] Although there have been no studies comparing the efficacy of single versus combination therapy, some investigators recommend combination therapy based on more rapid CSF sterilization and possible reduction of long-term neurological sequelae.

In the management of coccidioidal meningitis, most patients are now treated initially with fluconazole; in one study the response rate was 79%, although 24% of patients

exhibited a persistent CSF pleocytosis despite the relative absence of symptoms.[29] On the basis of these results, fluconazole (800–1200 mg daily) is recommended as first-line therapy for coccidioidal meningitis;[28,29,31] itraconazole and voriconazole can be considered as alternative agents, although few data are available. Therapy may need to be continued indefinitely. In patients who fail azole therapy, amphotericin B deoxycholate may be administered both intravenously and intrathecally. Intrathecal administration may be via the lumbar, cisternal or ventricular route (i.e. through an Ommaya reservoir). The usual dosage is 0.5 mg three times weekly for 3 months, although 1.0–1.5 mg combined with hydrocortisone can be used. Antifungal therapy is discontinued once the CSF has been normal for at least 1 year on an intrathecal regimen of once every 6 weeks.

Adjunctive therapy

Increased intracranial pressure and hydrocephalus have been noted in AIDS patients with cryptococcal meningitis. In patients with symptoms of increased intracranial pressure and CSF pressure $\geq$25 cmH_2O during induction therapy, relief of CSF pressure by lumbar puncture is recommended; persistent elevations may require repeat lumbar puncture daily or consideration of temporary placement of a percutaneous lumbar drain or ventriculostomy.[30] Permanent ventriculoperitoneal shunting should be utilized only if the patient has received appropriate antifungal therapy and if more conservative measures to control elevated intracranial pressure have failed.

Focal central nervous system infections

Brain abscess

Epidemiology and aetiology

Bacterial brain abscesses may be due to a single organism or may be polymicrobial in origin.[32] Clues to the likely aetiological agents may be found in the patient's history. Streptococci (aerobic, anaerobic and microaerophilic) are identified in up to 70% of patients. They are normal inhabitants of the oral cavity, gastrointestinal tract and female genital tract. Although streptococcal brain abscesses are seen most often in patients with otopharyngeal infections or infective endocarditis, they are isolated after neurosurgical or other medical procedures. Staphylococci are found in 10–20% of patients, usually those with a history of trauma or injection drug use. *Bacteroides* and *Prevotella* species are identified in 20–40% of patients, often in mixed cultures. Enteric Gram-negative bacilli are isolated in 23–33% of patients with brain abscess, often in patients with otitic foci of infection, septicaemia, following neurosurgical procedures or in those who are immunocompromised. Other bacteria (*S. pneumoniae, H. influenzae* and *L. monocytogenes*) are seen much less frequently (<1% of cases). Patients with defects in cell-mediated immunity (e.g. patients with AIDS, transplant recipients and those receiving corticosteroids) have an increased incidence of brain abscess caused by *Nocardia* species. *Mycobacterium tuberculosis* and non-tuberculous mycobacteria have been increasingly observed to cause focal CNS lesions, with several cases reported in patients with HIV infection.

Brain abscesses caused by *Aspergillus* species are seen in patients with haematological malignancies and those with prolonged neutropenia; other risk groups include patients with Cushing syndrome, diabetes mellitus and hepatic disease.[32,33] Risk factors for development of cerebral mucormycosis include patients with diabetes mellitus (especially in association with diabetic ketoacidosis), haematological malignancies, transplant recipients and corticosteroid or deferoxamine use. Infection caused by either agent may result from direct extension of rhinocerebral disease or from haematogenous spread from a distant focus of infection.

Clinical presentation

Symptoms in patients with bacterial brain abscess result from the presence of a space-occupying lesion and include headache (~70% of cases), nausea, vomiting and seizures.[32] Many patients also experience a change in mental status, ranging from lethargy to coma. Fever is found in only 45–50% of patients. Sudden worsening of the headache, accompanied by a new onset of meningismus, may signify rupture of the abscess into the ventricular space. The clinical presentation also depends upon the location of the abscess. Frontal lobe involvement may result in headache, drowsiness, inattention, hemiparesis, and/or motor disorders. Ataxia, nystagmus and vomiting indicate a cerebellar lesion, while an abscess of the temporal lobe produces headache, aphasia and visual field defects. Involvement of the brainstem may result in cranial nerve palsies, headache, fever and vomiting.

Fungal brain abscesses often present with symptoms similar to those of bacterial brain abscess (see the preceding text).[32,33] However, some differences do exist. *Aspergillus* species have a tendency to invade blood vessels and patients may present with signs and symptoms of cerebral infarction. In patients with rhinocerebral mucormycosis, symptoms may be referable to the eyes and sinuses in which patients present with headache, diplopia and nasal discharge. Physical examination may show nasal ulcers or discharge, proptosis, and/or external ophthalmoplegia. Approximately 60% of patients will have orbital involvement and there is an increased incidence of development of cavernous sinus thrombosis.

Diagnosis

Radiological techniques, such as CT and MR, have revolutionized the diagnosis of brain abscess.[32] CT

characteristically reveals a hypodense lesion with peripheral ring enhancement; there may also be a surrounding area of decreased attenuation due to cerebral oedema. MR offers significant advantages over CT in the diagnosis of brain abscess, including early detection of cerebritis, detection of cerebral oedema with greater contrast between oedema and the brain, more conspicuous spread of inflammation into the ventricles and subarachnoid space and the earlier detection of satellite lesions. Contrast enhancement with the paramagnetic agent gadolinium diethylenetriaminepentaacetic acid provides the added advantage of clearly differentiating the central abscess, surrounding enhancing rim and cerebral oedema surrounding the abscess.

In abscesses caused by *Aspergillus* species, radiographic studies (CT or MR) may show evidence of infarction with surrounding abscess formation. In mucormycosis, there may be bony erosion, sinus opacification and evidence of cavernous sinus thrombosis.

CT has also been useful to permit stereotactic guided aspiration of brain abscesses to obtain tissue for microbiological diagnosis.[32] Samples should be sent for Gram stain, aerobic and anaerobic culture and smears and cultures for AFB and fungi. If there is a clinical suspicion of *Nocardia* infection, a modified AFB stain should also be done. Recently, the use of multiple 16S ribosomal DNA sequences was found to increase dramatically the number of infectious agents identified in cerebral abscesses,[34] although confirmation of this study is needed to determine whether these agents are true pathogens in patients with brain abscess. Tissue should also be sent for histopathological examination. Definitive diagnosis in fungal brain abscess is based on biopsy or resection of the lesion, with a characteristic appearance of the causative organism in microbiological and histopathological specimens.

Therapy

Empirical antimicrobial therapy for bacterial brain abscess should include agents active against streptococci, anaerobes, the Enterobacteriaceae and staphylococci, although therapy can usually be chosen on the basis of the likely pathogenic mechanism of brain abscess formation (Table 117.3).[32] Optimal therapy of brain abscesses includes surgical intervention with either stereotactic CT-guided aspiration or craniotomy with resection or debridement; all lesions >2.5 cm in diameter should be excised or stereotactically aspirated. Certain patients may be treated with medical therapy alone and these criteria include the presence of multiple abscesses, location in a surgically inaccessible area, clinical improvement with medical therapy alone and abscess size ≤ 2.5 cm. Once culture results are available, antimicrobial therapy may be adjusted for optimal therapy (Table 117.4). Intravenous therapy for 6–8 weeks is recommended for treatment of bacterial brain abscess, often followed by 2–3 months of oral therapy (although the efficacy and necessity of this approach have not been established). Brain abscess caused by *Nocardia* species should be treated for up to 12 months, in conjunction with surgical resection.

The optimal therapy of fungal brain abscess requires a combined medical and surgical approach.[32,33] High-dose amphotericin B deoxycholate (0.8–1.25 mg kg^{-1} per day, with doses up to 1.5 mg kg^{-1} per day depending on the clinical response) was previously recommended for treatment of *Aspergillus* brain abscess. Voriconazole is now the drug of choice, with response rates of ~35%.[35] Mucormycosis should be treated with amphotericin B deoxycholate or one of its lipid formulations, along with correction of underlying metabolic derangements and aggressive surgical debridement.

Table 117.3 Empirical antimicrobial therapy of bacterial brain abscess.

Predisposing condition	Usual bacterial isolates	Antimicrobial regimen
Otitis media or mastoiditis	Streptococci (anaerobic or aerobic), *Bacteroides* and *Prevotella* species, Enterobacteriaceae	Metronidazole + a third-generation cephalosporin[a]
Sinusitis (frontoethmoidal or sphenoidal)	Streptococci, *Bacteroides* species, Enterobacteriaceae, *Staphylococcus aureus, Hemophilus* species	Metronidazole + a third-generation cephalosporin[a,b]
Dental sepsis	Mixed *Fusobacterium* and *Bacteroides* species, streptococci	Penicillin + metronidazole
Penetrating trauma or postneurosurgical	*Staphylococcus aureus*, streptococci, Enterobacteriaceae, *Clostridium*	Vancomycin + a third-generation cephalosporin[a]
Lung abscess, empyema, bronchiectasis	*Fusobacterium, Actinomyces, Bacteroides* species, streptococci, *Nocardia asteroides*	Penicillin + metronidazole + a sulfonamide[c]
Bacterial endocarditis	*Staphylococcus aureus*, streptococci	Vancomycin + gentamicin

[a] Cefotaxime or ceftriaxone; ceftazidime or cefepime is used if *Pseudomonas aeruginosa* is suspected.
[b] Add vancomycin if infection caused by methicillin-resistant *Staphylococcus aureus* is suspected.
[c] Sulfadiazine or trimethoprim–sulfamethoxazole; include if *Nocardia asteroides* is suspected.

Table 117.4 Antimicrobial therapy of brain abscess.[a]

Organism	Standard therapy	Alternative therapies
Actinomyces species	Penicillin G	Clindamycin
Aspergillus species	Voriconazole	Amphotericin B lipid complex; liposomal amphotericin B; amphotericin B deoxycholate
Bacteroides fragilis	Metronidazole	Clindamycin
Candida species	Amphotericin B deoxycholate + 5-flucytosine	Fluconazole
Enterobacteriaceae	Third-generation cephalosporin[b]	Aztreonam; trimethoprim–sulfamethoxazole; fluoroquinolone; meropenem
Fusobacterium species	Penicillin G	Metronidazole
Mucormycosis	Amphotericin B deoxycholate	Liposomal amphotericin B; amphotericin B lipid complex; posaconazole
Nocardia asteroides	Trimethoprim–sulfamethoxazole or sulfadiazine	Minocycline; imipenem; meropenem; third-generation cephalosporoin[b]; amikacin
Pseudomonas aeruginosa	Ceftazidime[c]or cefepime[c]	Aztreonam[c]; fluoroquinolone[c]; meropenem[c]
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin-resistant	Vancomycin	Trimethoprim–sulfamethoxazole
Streptococcus milleri, other streptococci	Penicillin	Third-generation cephalosporin[b]; vancomycin

[a]Depending upon the pathogenesis of bacterial brain abscess, these bacteria may be part of a mixed infection and treatment for other suspected bacteria should be given.
[b]Cefotaxime or ceftriaxone.
[c]Addition of an aminoglycoside should be considered.

Subdural empyema

Epidemiology and aetiology

The most common predisposing conditions to cranial subdural empyema are otorhinological infections; 50–80% of cases begin in the paranasal sinuses.[36] Other predisposing conditions include skull trauma, neurosurgical procedures and infection of a pre-existing subdural empyema; haematogenous dissemination occurs in only about 5% of cases. The bacterial species isolated from cranial subdural empyema include streptococci (~25–45%), staphylococci (~10–15%) and aerobic Gram-negative bacilli (~3–10%); anaerobes (e.g. anaerobic and microaerophilic streptococci *Bacteroides fragilis*) have been recovered in up to 100% of cases. Polymicrobial infections are common.

Clinical presentation

Subdural empyema can present as a rapidly progressive, life-threatening infection with symptoms and signs related to the presence of increased intracranial pressure, meningeal irritation, and/or focal cortical inflammation.[36] A prominent complaint is headache, which is initially localized to the infected sinus or ear but becomes generalized as the infection progresses. Other clinical findings include vomiting, altered mental status (with progression to obtundation if treatment is not initiated), fever and focal neurological signs (usually within 24–48 h with rapid progression). About 80% of patients have meningeal irritation and seizures occur in more than half of cases. Without treatment, there is a rapid neurological deterioration with signs of increased intracranial pressure and cerebral herniation. However, this fulminant presentation may not be seen in patients with cranial subdural empyema following cranial surgery or trauma, in patients who have received prior antimicrobial therapy, in patients with infected subdural haematomas or in patients with infections metastatic to the subdural space.

Diagnosis

The diagnostic procedure of choice for cranial subdural empyema is either CT with contrast enhancement or MR imaging.[36] CT typically reveals a crescentic or elliptically shaped area of hypodensity below the cranial vault or adjacent to the falx cerebri; with extensive disease, there is often associated mass effect. Following the administration of contrast material, there is a fine, intense line of enhancement that can be seen between the subdural collection and cerebral cortex. Extensive mass effect, manifested as ventricular compression, sulcal effacement and midline shift, is invariably present. MR provides greater clarity of morphological detail than CT and is particularly valuable in detecting subdural empyemas located as the base of the brain, along the falx cerebri or in the posterior fossa. MR can also differentiate empyema from most sterile effusions and

chronic haematomas, making it the diagnostic modality of choice for subdural empyema.

Therapy

The therapy of subdural empyema requires a combined medical and surgical approach because antimicrobial agents alone do not reliably sterilize these lesions and surgical decompression is needed to control increased intracranial pressure.[36] Drainage via burr hole placement may be considered in the early stages of subdural empyema when the pus is liquid, although it may not be adequate in 10–20% of patients. For patients requiring craniotomy, a wide exposure should be afforded to allow adequate exploration of all areas of suspected infection. In one report,[37] craniotomy appeared to be superior to burr hole and craniectomy drainage, as patients undergoing burr hole or craniectomy drainage not only required more frequent operations to drain recurrent or remaining pus, but also exhibited higher mortality rates and poorer outcomes.

Following the aspiration of purulent material, antimicrobial therapy is based on the results of Gram stain and predisposing condition. If the primary infection is paranasal sinusitis, otitis media or mastoiditis, therapy with vancomycin, metronidazole and a third-generation cephalosporin (cefotaxime or ceftriaxone; or ceftazidime, cefepime or meropenem if *P. aeruginosa* is suspected) is recommended pending organism identification. Parenteral therapy should be continued for 3–4 weeks and perhaps longer if an associated osteomyelitis is present,[36] although there are no firm data to support a specific duration of antimicrobial therapy in patients with subdural empyema.

Epidural abscess

Epidemiology and aetiology

Epidural abscess refers to a collection between the dura mater and the overlying skull or vertebral column.[36,38] The aetiologies of cranial subdural abscess are usually the same as for subdural empyema (see the preceding text), whereas spinal epidural abscess usually follows haematogenous dissemination from foci elsewhere to the epidural space (25–50% of cases) or by extension from a vertebral osteomyelitis, local trauma or infection (e.g. from penetrating trauma, decubitus ulcers, paraspinal abscess, back surgery, lumbar puncture or epidural anaesthesia). The likely infecting organisms in spinal epidural abscess are staphylococci (50–90%), streptococci (8–17%) and aerobic Gram-negative bacilli (12–17%).

Clinical presentation

Symptoms in patients with cranial epidural abscess are usually insidious, with the presentation overshadowed by the primary focus of infection (e.g. sinusitis or otitis media).[36,38] Cranial epidural abscesses usually enlarge too slowly to produce sudden major neurological deficits unless there is deeper intracranial extension. The typical complaints are fever and headache, focal neurological signs, seizures and papilloedema and other signs of increased intracranial pressure may eventually develop without appropriate therapy.

In contrast, spinal epidural abscess may develop rapidly within hours (following haematogenous dissemination) or pursue a chronic course over months (associated with vertebral osteomyelitis).[36,38] Initially, patients complain of focal vertebral pain (the most consistent symptom seen in 70–90% of patients), followed by root pain, defects of motor, sensory or sphincter function and finally paralysis. These symptoms and signs indicate the need for emergency evaluation, diagnosis and treatment.

Diagnosis

MR imaging is the diagnostic procedure of choice for both cranial and spinal epidural abscess.[36] In cases of spinal epidural abscess, MR is recommended because it can visualize the spinal cord and epidural space in both the sagittal and transverse sections and can also identify accompanying osteomyelitis, intramedullary spinal cord lesions and joint space infection.

Therapy

Recommendations for antimicrobial therapy for cranial epidural abscess are the same as for subdural empyema (see the preceding text). Presumptive therapy for spinal epidural abscess must include an antistaphylococcal agent (i.e. vancomycin); coverage for Gram-negative bacilli (e.g. ceftazidime, cefepime or meropenem) must be included for patients with a history of a spinal procedure or injection drug use.[36,38]

Antimicrobial therapy for an uncomplicated spinal epidural abscess should be continued for 4–6 weeks and for 6–8 weeks if osteomyelitis is present. Surgical therapy for epidural abscess is aimed at drainage of the collection and for patients with neurological changes to minimize the likelihood of permanent neurological sequelae. Some patients with spinal epidural abscess have been treated with antimicrobial therapy alone (i.e. those with an unacceptably high surgical risk or those without neurological deficits), although these patients must be carefully followed for clinical deterioration and for progression by radiological studies.[36,38] Surgical decompression should be performed in patients with increasing neurological deficit, persistent severe pain, increasing temperature or peripheral white blood cell count. Surgery is not likely to be a viable therapeutic option in patients who have experienced complete paralysis for more than 24–36 h, although some would perform surgical therapy in patients with duration of complete paralysis of less than 72 h.

Encephalitis

Encephalitis is characterized by symptoms similar to those seen with acute meningitis, but patients with encephalitis are more likely to experience mental status changes and seizures. Numerous infectious and non-infectious aetiologies may produce encephalitis.[39] Most common are the herpes viruses that are also the most treatable. West Nile encephalitis has been reported in endemic areas and is discussed below.

Herpes simplex virus

Epidemiology and aetiology

Herpes simplex virus accounts for ~10–20% of viral encephalitides and occurs sporadically throughout the year, affecting all age groups;[40] most cases in adults are caused by HSV type 1. The disease is associated with significant morbidity and mortality (as high as 70% if untreated).

Clinical presentation

Patients with HSV encephalitis often present with diminished levels of consciousness and focal neurological signs, such as dysphasia, weakness and paraesthesias.[40] Personality changes and fever are uniformly present and approximately two-thirds of patients develop seizures, often involving the temporal lobes. The clinical course may be slow or progress with alarming rapidity, with progressive loss of consciousness leading to coma.

Diagnosis

CSF examination in HSV encephalitis reveals a lymphocytic pleocytosis in 97% of cases with biopsy-proven disease and an elevated protein.[40] The presence of CSF red blood cells suggests the diagnosis but is not always present. Generally, CSF culture is of limited value.[5] Detection of HSV DNA in the CSF using PCR is both sensitive (96–98%) and specific (95–99%) and is now the optimal method for the diagnosis of HSV encephalitis.[39,40] However, an initially negative CSF PCR result for HSV may become positive if the test is repeated 1–3 days after initiation of treatment, such that in undiagnosed cases in which patients have clinical features of HSV encephalitis or temporal lobe lesions on neuroimaging, consideration should be given to repeating the PCR for HSV 3–7 days later on a second CSF specimen.[39] Several non-invasive tests may also support the diagnosis of HSV encephalitis. The electroencephalogram (EEG) may show a characteristic spike-and-slow wave activity with periodic lateralizing epileptiform discharges over the temporal and frontotemporal regions. MR is more sensitive than CT, revealing temporal lobe abnormalities in more than 90% of PCR-proven HSV encephalitis, and is considered by many experts to be the most important and specific imaging technique.

Antimicrobial therapy

On the basis of its ease of administration and good safety profile, treatment with intravenous acyclovir 30 mg kg^{-1} per day (in patients with normal renal function) in three divided doses for 14–21 days is recommended for patients with suspected HSV encephalitis.[39,40]

Varicella zoster virus

Epidemiology and aetiology

Herpes zoster is a consequence of reactivation of latent VZV and a direct correlation exists between cutaneous dissemination and visceral involvement (including meningoencephalitis).[27] CNS complications associated with recurrent zoster infection result in significantly higher morbidity and mortality than primary varicella infection. This may be due to the advanced age and underlying illnesses of most patients with herpes zoster.

Clinical presentation

Symptoms associated with CNS infection with VZV include headache, fever, vomiting, seizures, altered sensorium and focal neurological deficits.[27] Encephalitis is the most common abnormality associated with herpes zoster, seen most commonly in patients of advanced age, following immunosuppression and in those with disseminated cutaneous zoster. Some patients with ophthalmic zoster present with the distinctive CNS process of contralateral hemiplegia that usually occurs several weeks or more after zoster ophthalmicus; this finding is seen in up to one-third of CNS abnormalities in herpes zoster.

Diagnosis

CSF analysis in patients with herpes zoster encephalitis shows a lymphocytic pleocytosis and elevated protein, although these findings may be seen in up to 40% of zoster patients without CNS involvement.[27] Viral cultures are rarely helpful diagnostically. PCR detection of VZV DNA has a specificity of >95% but the sensitivity is 80–95%.[39] In patients with zoster ophthalmicus with contralateral hemiplegia, a unilateral arteritis or thrombosis of involved vessels may be seen on cerebral angiography and cerebral infarction may be seen on CT or MR imaging.

Antimicrobial therapy

Although no clinical trials have established the efficacy of antiviral therapy in herpes zoster encephalitis, we believe that intravenous acyclovir should be used in this setting.[39]

West Nile virus

Epidemiology and aetiology

West Nile encephalitis is an infection of the brain caused by West Nile virus (WNV), a flavivirus that is commonly found in Africa, West Asia and the Middle East. The virus first appeared in the USA in 1999 with an outbreak of meningoencephalitis reported in New York City.[41] Mosquitos are the primary vectors of WNV and anyone bitten by an infected mosquito can get the disease. It has been estimated that the risk to a person of becoming infected with WNV from the bite of an infected mosquito is about 1%. Transmission can also occur via transplanted organs and infected blood products. Most human infections with WNV are asymptomatic, but, in recent outbreaks, one in five infected persons developed West Nile fever and one in 150 developed CNS disease;[42] the elderly are much more likely to develop serious diseases. Although the risk of infection with WNV may be small, the disease can be fairly serious; mortality from WNV neuroinvasive disease is ~12%.

Clinical presentation

Patients with WNV encephalitis present with fever, headache, mental status changes, nausea and vomiting.[42] Severe generalized muscle weakness was a common feature in cases during the New York City outbreak, and also in other outbreaks in the USA. Seizures are uncommon. Depressed deep tendon reflexes, diffuse muscle weakness, flaccid paralysis and respiratory failure may also occur. The disease progresses to coma in about 15% of patients.

Diagnosis

CSF examination in patients with WNV encephalitis typically reveals a moderate lymphocytic pleocytosis (although no cells or neutrophils may be seen), elevated protein and normal glucose. Laboratories can perform an IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA). Using this assay, virus-specific IgM can be detected in nearly all CSF and serum specimens received from WNV-infected patients at the time of their clinical presentation.[39,42] However, the serum IgM antibody may persist for more than 1 year and physicians must determine whether the detection of antibody is the result of a WNV infection in the previous year and unrelated to the current clinical presentation. The IgM in the CSF is specific for CNS infection, with almost all patients having detectable antibody by the first week of presentation.

Treatment

There is no specific treatment for West Nile encephalitis.[39] In more severe cases, intensive supportive therapy is indicated, often involving hospitalization, intravenous fluids, airway management, respiratory support, prevention of secondary infections (e.g. pneumonia, urinary tract infection) and good nursing care.

Postpolio syndrome

Epidemiology

Any discussion of CNS infections in the elderly should include the postpolio syndrome. This syndrome does not appear to be because of persistent poliovirus infection, but rather is likely due to an age-related loss of surviving motor neurons and their inability to innervate the enlarged motor neuron units seen in poliomyelitis patients.[43] In a study of the prevalence and risk factors for postpolio syndrome in a cohort of 551 former poliomyelitis patients in Allegheny County, PA, 137 (~25%) developed symptoms of the postpolio syndrome between 32 and 39 years after the acute illness. Risk factors for the development of the postpolio syndrome were female gender, bulbar disease and the degree of post-recovery residual impairment. Despite the relatively high prevalence of this disorder, the majority of patients (80% in this study) did not require the use of new assisted devices to accomplish their activities of daily living, despite a subjective decline in their functional status.

Clinical presentation

The postpolio syndrome is characterized by muscle weakness, muscle and/or joint pain, fatigue and a decline in functional status occurring 30–40 years after acute poliomyelitis.[43] Some patients have progressive weakness and wasting in muscles that were not necessarily weak at the onset of poliomyelitis.

Diagnosis

Conventional electromyography (EMG) demonstrates chronic denervation; occasionally there may also be new or ongoing denervation manifested as fasciculations, fibrillations and positive sharp waves.[43] Enlarged motor units consistent with highly increased fibre density can be demonstrated in 90% of patients on single-fibre EMG. However, the primary role of EMG is to exclude other causes of the patient's presentation.

Therapy

There is no definitive treatment for the postpolio syndrome, but symptomatic improvement may be obtained with analgesics such as paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs (NSAIDs), local heat application to affected muscles and joints and a low-impact, non-fatiguing exercise programme to prevent the development of muscle atrophy.[43] Patients may also benefit from rest periods, increased sleep time and other energy conservation methods to overcome fatigue.

Creutzfeldt–Jakob disease

Epidemiology

The most common human prion disease is sporadic, or classic, Creutzfeldt–Jakob disease (CJD), with a worldwide incidence of approximately one case per million population;[44] however, among individuals aged 60–74 years, the incidence is five cases per million population. Symptoms generally begin by age 60–70 years, with a mean age of onset of 60 years.

Clinical presentation

Sporadic CJD is characterized by a rapidly progressive multifocal neurological dysfunction, myoclonus and a terminal state of global severe cognitive impairment.[44] About 40% of patients with sporadic CJD present with rapidly progressive cognitive impairment, 40% with cerebellar dysfunction and the remaining 20% with a combination of both findings. The clinical picture rapidly expands to include behavioural abnormalities, higher cortical dysfunction, cortical visual abnormalities, cerebellar dysfunction and both pyramidal and extrapyramidal signs. Almost all patients with sporadic CJD develop myoclonus that involves either the entire body or a limb; myoclonus may be absent at disease onset, but appears with increasing severity as the disease progresses. After a rapidly progressive illness of 3–9 months, death usually occurs with the patient in an akinetic and mute state.

Diagnosis

The clinical presentation, progressive nature and failure to find any other diagnoses are the hallmarks of sporadic CJD. There are no available, completely reliable diagnostic tests for use before the onset of clinical symptoms in patients with sporadic CJD. During the course of disease, most patients develop a characteristic picture on EEG with periodic paroxysms of sharp waves or spikes on a slow background.[44] These periodic complexes have a diagnostic sensitivity and specificity of 67% and 87%, respectively, on a single EEG; if repeated recordings are obtained, more than 90% of patients show periodic EEG abnormalities. The triad of myoclonus, dementia and EEG periodic sharp waves is a characteristic presentation of sporadic CJD.

Therapy

There is no treatment that can cure or control CJD. About 90% of patients die within 1 year.[44] Current treatment is aimed at alleviating symptoms and making the patient as comfortable as possible. Opiate drugs can help relieve pain; clonazepam and sodium valproate may help relieve involuntary myoclonus. Quinidine has been tested in an uncontrolled and unblinded study of patients with sporadic CJD; despite transient improvement in some patients, they reverted to their previous states and died of progressive disease.

Key points

- Central nervous system infections are frequently devastating and can lead to significant morbidity and mortality.
- Although the brain possesses several defence mechanisms to prevent infection, once microorganisms reach the central nervous system, host defence mechanisms are inadequate to control the infection.
- Antimicrobial therapy is limited by the poor penetration of many agents into the central nervous system.
- Recent developments in diagnosis and therapy of meningitis, brain abscess, subdural empyema, epidural abscess, encephalitis, postpolio syndrome and Creutzfeldt–Jakob disease are reviewed.
- The use of adjunctive treatment strategies is discussed.

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SECTION 15

Special Issues

CHAPTER 118

Elder abuse: a UK perspective

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History of elder abuse management in the UK

In 1975, when Alex Baker coined the phrase 'granny battering', there was relatively little interest in elder abuse in the UK.[1] By 1989, professionals were becoming interested and the first multidisciplinary conference on elder abuse in the UK was held by the British Geriatrics Society.[2] By 1991, Virginia Bottomley, the then Minister for Health, was still informing the House of Commons that it was not a major issue. The UK charity Action on Elder Abuse was formed in 1993 and the Department of Health issued guidance on elder abuse in 2000 (*No Secrets*[3]). In 2004, a House of Commons Health Committee report proposed changes to care home inspection, regulation of care staff and the introduction of mandatory training in elder abuse recognition for professionals working with older people.[4]

In England and Wales, guidance on management of abuse is outlined in *No Secrets*[3] and *In Safe Hands*[5], respectively. In 2008–09, the Department of Health launched a consultation into this guidance, asking whether adult safeguarding should be placed on a statutory footing. In Scotland, the Adult Support and Protection Act (2007) has already made adult protection statutory. This Act created new measures to protect adults believed to be at risk of harm. These include rights of entry to places where adults are thought to be at risk, a range of protection orders including assessment, removal of the adult at risk and banning of the person causing the harm; and supporting the creation of multidisciplinary adult protection committees. In Northern Ireland there is no specific guidance or legislation relating to the management of suspected elder abuse.

Defining elder abuse

Elder abuse is defined as a violation of a vulnerable older person's human and civil rights by another person(s).[3,5] This definition specifies that these acts are abuse when they happen to a 'vulnerable person'. Older people are more likely to be vulnerable due to more physical and cognitive impairments, but there is nothing inherently different about how abuse should be identified and managed in younger and older adults, and they are protected by the same guidelines and legislation.[4] Like domestic violence, elder abuse can also occur in an older person who is physically well and has mental capacity.

Different types of abuse are recognized. Verbal or psychological abuse encompasses acts such as screaming and shouting at an older person, calling them names, threatening, humiliating or 'scapegoating' them. Physical abuse includes non-accidental use of force against an older person, such as hitting, shoving or handling them roughly in other ways, and also inappropriate use of medication, restraint or confinement. The over-prescription and use of as-required medication has attracted considerable attention of late in the UK. Around 100 000 older people in UK care homes are prescribed antipsychotic drugs, often in the absence of psychotic symptoms.

Neglect is defined as ignoring medical or physical care needs, failure to provide access to appropriate health or social care or withholding of the necessities of life, such as medication, adequate nutrition and heating. Financial and sexual abuse involve persuading someone to enter into a financial or sexual transaction to which he or she has not consented or cannot consent. Finally, discriminatory abuse is defined as harassment, slurs or other abusive behaviour towards an older person because of age, race, gender, disability, sexual preferences or other personal characteristics.

Among people providing care, there is often a lack of consensus about what constitutes abuse. While health professionals, family carers and older people are likely to agree that the most serious types of abuse, such as physical violence, should be defined as such, there is often less agreement about other types of behaviour. For example, while locking a person with dementia in their house all day alone to prevent wandering would constitute abuse according to *No Secrets*, less than two-thirds of English family

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

carers, medical students and mental healthcare professionals thought that this scenario was abuse when presented with it in a vignette.[6,7]

Most people agree that behaviour has to reach a certain threshold of severity or frequency to constitute abuse. Shouting at someone angrily once, for example, may be accepted within all emotional relationships. Although the parameters change when one member is dependent and vulnerable, this does not mean that such actions automatically constitute abuse. Most abuse measures use cut-points for how frequently a behaviour must be reported to be considered abusive. For example, the Pillemer criteria define abuse caseness as verbal or neglectful acts occurring ≥ 10 times per year and physical or financially abusive acts at least once per year.[8] The Modified Conflict Tactics Scale (MCTS) asks whether abusive acts have happened never, almost never, sometimes, quite frequently or almost always, and defines an 'abuse case' as an abusive act happening at least *sometimes* in the last 3 months.[9]

In clinical practice, standardized measures of abusive behaviour are not generally used and there is variation among clinicians regarding the thresholds for considering behaviour abusive and for acting on these concerns. Thinking about abuse as either happening or not can lead to an 'all or nothing' response (social services referral of only most serious cases and ignoring others). Detecting and actively managing behaviour that is less severe in nature and frequency may lead to help being given before the problem becomes more serious.

Prevalence of elder abuse

Elder abuse is inherently difficult to study. It is a hidden offence, often perpetrated against vulnerable people (many with memory impairment), by those on whom they depend. Prevalence estimates are influenced, and possibly underestimated, by the fact that many older people are unable, frightened or embarrassed to report its presence. Prevalence estimates of abuse vary greatly between studies and this is partly explained by the different thresholds used to define significant abuse. In the 2007 CARD (Caring for Relatives with Dementia) study of family carers of people with dementia recruited from English old-age psychiatric services, the 3 month prevalence of significant abuse reported by carers against the person they were caring for, as defined by a screening instrument, was 34%, but when we asked a panel of old-age psychiatrists to review the carers' responses, they agreed that they would be clinically concerned in 6.8% of cases.[10] The act of abuse does not imply intent and in many cases the carers may not have viewed their own actions in this light.

Rates of abuse are particularly high among vulnerable people, including those with dementia. Around one-quarter of vulnerable older people (e.g. those receiving home care services) reported significant levels of psychological abuse. Rates of elder abuse in UK care homes have not been studied, although in other Western countries, one in six care home staff admit psychologically abusing people in their care and four-fifths observing abuse if asked.

When health professionals or researchers look for evidence of abuse as opposed to asking older people about it, they find less, nearer 5% in vulnerable older people, probably because they are only detecting more serious physical abuse or neglect with physical evidence. The number of abuse cases reported to authorities is low. Unlike in the USA, the UK does not have a system of mandatory reporting of all abuse and neglect cases, so data are not widely available from about the prevalence of cases of elder abuse reported to social services.

The prevalence of abuse in the older general population is lower than in vulnerable groups. Around 5% reported significant abuse over a period of 1 month. Most of this is psychological, verbal and/or financial abuse.[11] In the largest UK survey of elder abuse to date, 4% of older people living in private homes reported abuse. People with cognitive impairment were excluded from this survey.[12]

Risk factors for elder abuse

The causes of abuse are complex and varied. Older people who are more dependent because of physical or cognitive impairment are more at risk of abuse. In addition to requiring more care, they are less able to leave or report an abusive situation. Older people with mental health problems, who are more depressed or have suicidal thoughts, also report more abuse.

Providing care is physically and emotionally demanding. Family carers who are more anxious and depressed are more likely to act abusively towards the person they care for, as are those who use unhelpful coping strategies such as substance use and denial in response to stress or resent their caring role.[13] Family carers who live with the person they care for and have fewer breaks are more likely to report acting abusively.[14] Carer stress is less likely to explain other types of abuse (financial and sexual abuse) which could not be perceived as reactions to the high stress of caring. Professional carers who report high levels of carer stress and burnout are also more likely to report acting abusively.

Abuse is not a one-way phenomenon. Being on the receiving end of abuse is one of the most important predictors of carers acting abusively.[13] Relationships that were previously psychologically or physically violent with acts being perpetuated by both members of the dyad may become abusive if the care recipient no longer has the mental capacity to decide whether or not to stay in a violent relationship

or the physical capacity to leave it and live independently. People who lack a close confidant and are socially isolated are more at risk of abuse.

A minority of abuse is sadistic in nature. A few professionals may choose to work in a setting where they have power in order to abuse. There is very little evidence about who is most likely to perpetrate or be a victim of this abuse, which is probably common in the most severe abuse cases. Feelings emanating from the staff member's experiences of caring and being cared for within their own family may affect how they behave in their professional caring role, including whether they behave abusively. Sadomasochistic traits may come to the fore in the unequal power relationship between patients and staff.[15]

Abuse in institutions

The best available evidence for institutional characteristics associated with abuse comes from inquiries conducted into abuse scandals. Prominent inquiries include an investigation into physical and emotional abuse of patients by care staff on Rowan ward in Manchester in 2002[16] and physical mistreatment of older people who were mentally frail by staff at Beech House in London over a 3 year period (1993–96). The following factors were thought to be important in fostering an environment in which abuse could occur and remain undetected for some time: a poor and institutionalized environment, low staffing levels with high use of bank and agency staff and little staff development and poor supervision, a lack of knowledge of incident reporting, closed inward-looking culture, weak management at ward and locality level, low staff morale and lack of involvement by relatives in care delivery, decision-making and evaluation of the service.

Detecting abuse

The best way of detecting verbal, psychological and less severe abuse is to ask older people and their carers about it in a sensitive and non-judgemental way. When we recently asked family carers questions about abuse from the Modified Conflict Tactics Scale, 97% found the questions acceptable.[17] This scale includes questions about psychologically and physically abusive acts.

Screening for objective signs of abuse is only likely to detect the most serious abuse, but this may be abuse that is not volunteered when asked. Detecting abuse is difficult when the victim cannot say what is happening. It is important to take note of changes in behaviour, unusual distress and any previous history of allegations. Unexplained bruising, especially if the distribution is inconsistent with the history or likely causes of accidental bruising, finger marks, burns or untreated sores may be evidence of physical abuse.

More serious neglect is likely to be evident from visiting an older person's home and medical examination. Risk markers include dirty or inappropriate clothing, poor personal hygiene, evidence of malnourishment or dehydration, poor skin integrity, bruising or lacerations, contractures, urine burns/excoriations, diarrhoea or faecal impaction and reports of being left in an unsafe situation or inability to get needed medications.[18] These do not differentiate between a person who has a previously unidentified need for increased care, is refusing to accept care that is offered, and someone who is being neglected, and urgent social investigation will be needed to explore the situation.

Relatives may raise concerns about paid carers or other relatives financially abusing an older person or the older person who does not understand the value of money paying too much or giving away money they cannot afford. Suspicion may be aroused if the older person appears to have financial problems disproportionate to their income, no money available or if a relative appears to be encouraging them to make a financial transaction (e.g. selling their house) which appears unwise.

Abuse is often known about by other professionals or family members. It may go unacknowledged if they feel there are no better management options. In a recent meta-analysis, only one-third of professionals working with older people had detected a case of abuse in the last year and only half of detected abuse was reported.[19] This is surprisingly low given that one-quarter of vulnerable adults report abuse in surveys. Staff who detect abuse may not report it because they are unclear about the procedures to do so or because they empathize with the perpetrator, fear recrimination or believe that procedures designed to deal with it are inappropriate and punitive.[20] Inquiries into abuse scandals have found that abuse was known about and sometimes reported months or years before decisive action was taken to stop it.

It is important that staff are trained about what constitutes abuse, how to recognize it and who to report it to. In a study based in a London mental health trust, an educational intervention increased staff knowledge about how to detect and manage abuse, whereas giving staff the same information in a written format did not.[21] Having whistle-blowing policies that are well publicised can also help to increase detection of abuse in care organizations. In UK law there is no protection of anonymity for staff who raise concerns about malpractice at work (whistle-blowing), but there is protection against victimization and loss of employment as a result of raising a genuine concern.

Management of abuse

All health and social care professionals have a responsibility to act on any suspicion or evidence of significant abuse or

neglect. They should contact the local social services to make an 'adult protection' referral. Arrangements are in place throughout the UK for responding to all allegations of abuse against 'vulnerable' adults. Some types of abuse, including assault (sexual or physical), theft and fraud, are criminal offences under UK law and should be reported to the police. Professionals should refer all cases where they think significant harm might be occurring or there is a future risk of significant harm. The UK law commission suggests that 'harm' should be taken to include not only ill treatment (including sexual abuse and all forms of ill treatment that are not physical), but also the impairment of, or an avoidable deterioration in, physical or mental health.

Patients should usually be informed that a referral is to be made to social services if they are able to understand this, unless doing so would increase their distress or the risk of harm to them. Occasionally they may object, in which case professionals should consider whether they have the capacity to make this decision. Any intimidation, misuse of authority or undue influence will have to be assessed in making this judgement. Even if an adult has the capacity to refuse consent for an investigation into any alleged abuse, it may still be necessary to override this if other vulnerable adults are at risk. An initial rejection of help should not always be taken at face value.

Once an adult protection referral is received, social services will record the precise factual details of the alleged abuse, coordinate the investigation and come to a decision. Decisions may be made at a case conference. Actions as a result of an investigation may be supportive or therapeutic, disciplinary action or deregistration for professionals or, in a small minority of very serious cases, criminal prosecution. In England and Wales, the Mental Capacity Act (2005) introduced a new, arrestable criminal offence of ill-treatment or neglect of a person without capacity.

Social services seek the least disruptive, safe option for the older person in managing abuse, and where abuse is less severe, support services may be increased or the carer referred for support in their own right to see if this alleviates the situation. It is logical that if abuse often arises from stress among family carers, then interventions to reduce stress may reduce abusive behaviour. A handful of studies have sought to reduce abuse in this way, but as yet there have been no randomized controlled trials that would provide good evidence that this approach works.

Older people with capacity may decline assistance and refuse interventions deemed appropriate, such as moving to alternative accommodation. People with capacity have the right to make decisions that involve risk. Services have a responsibility in these circumstances to ensure that such risk is recognized and understood by all concerned and minimized whenever possible.

In addition to social services, allegations of abuse made against care professionals are also investigated by the Social Care Inspections bodies (Care Quality Commission in England, Scottish Care Commission, Care and Social Services Inspectorate for Wales and the Northern Ireland Department of Health, Social Services and Public Safety) or for NHS services, the Primary Care Trust. The Protection of Vulnerable Adults (POVA) scheme was introduced for registered care homes and domiciliary care services in 2004 in England and Wales. If there are reasonable grounds to suspect that an employee or ex-employee is guilty of harming or placing at risk of harm a vulnerable adult, a POVA list referral should be made by their employer. This is in addition to usual disciplinary procedures. If appropriate, this person will then be put on the POVA list, to prevent them securing further work with vulnerable adults. Similarly, if there are reasonable grounds to suspect that a health or social care professional has placed a vulnerable adult at significant risk of harm, this should be reported to their regulatory body. Abuse (including physical, verbal or sexual abuse of patients and theft from patients) currently constitutes just under one-third of fitness to practice charges reported to the Nursing and Midwifery Council.

Preventing abuse

It is now policy that all new staff working with children and vulnerable adults in England, Wales and Northern Ireland have a Criminal Records Bureau (CRB) check to ensure that there is no known reason why an individual should not work with these client groups. In Scotland, these disclosures are managed by Disclosure Scotland. Work is under way to register all people working in domiciliary or residential care settings with vulnerable adults with the UK General Social Care Councils for England, Wales, Scotland and Northern Ireland, which were set up in 2001. They facilitate training and enforce their code of practice. Alongside the POVA list, registration will help prevent people who have been found guilty of abuse or neglect being retained in the workforce.

Regular training and supervision of staff help prevent abuse. This is both because people are less likely to commit abusive acts if they are likely to be detected, but also because staff who are referred for disciplinary procedures due to allegations of abuse often do not know their acts would be perceived in this light or may have wanted help but not known who to turn to.

Conclusion

About 5% of elderly people aged 65 years and over and one-quarter of vulnerable elderly people report a recent episode of elder abuse. Older people who are dependent on care from others or live in care homes are at particular risk. When a carer feels stressed they are more likely to abuse the elderly person for whom they are caring. There

are currently no evidence-based interventions to reduce abusive behaviours by family carers and we think that the development of these is an urgent next step.

Since the early 1990s, awareness of the prevalence of elder abuse has grown. Prevention initiatives include the registration of all people working in domiciliary or residential care settings with vulnerable adults with the General Social Care Councils and the Protection of Vulnerable Adults list to prevent professionals who abuse from working elsewhere. Social services are the lead agency for managing elder abuse throughout the UK. Reporting of elder abuse is not mandatory in the UK so there are no national figures for the number of cases reported to adult social services, but it is very likely that reported cases are 'the tip of the iceberg'.

Key points

- Elder abuse is defined as a violation of a vulnerable older person's human and civil rights by another person(s).
- In contrast, neglect is defined as ignoring medical or physical care needs, failure to provide access to appropriate health or social care or withholding of the necessities of life, such as medication, adequate nutrition and heating.
- Older people who are more dependent because of physical or cognitive impairment are more at risk of abuse.
- Abuse is often known about by other professionals or family members.

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CHAPTER 119

Good quality care: abuse

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The empire of old age is spreading its influence. But beyond increased life expectancy at birth, some new situations are emerging. Through medical progress, some deadly diseases have become chronic illnesses (e.g. cancer, AIDS), but other conditions have made themselves at home, such as disabling illnesses and Alzheimer's disease. This epidemiological admission must be completed by an understanding of the problems that handicapped ageing raises.

The insufficient financial resources of some pensioners represent another characteristic. In France, the average pension of a retiree is 1100 euros per month, but the average cost in a retirement home is between 2200 and 2500 euros per month.

Medical and economic factors can contribute to vulnerable situations, which can lead to maltreatment. This has been the French experience.

Definitions

Abuse is an acknowledged deviance. According to the Council of Europe's definition, 'Abuse consists of all and any acts or omissions, which endanger one's life, threatens bodily or psychological integrity or infringes one's liberty or compromises personality development and/or seriously undermines financial security'.

As is well known, those who are vulnerable represent the usual target. Handicapped and dependent people and especially cognitive disorders represent vulnerable clinical situations.

The fight against abuse of the vulnerable elderly has become a social and ethical issue. On a semantic level, 'good quality care' is not the opposite of 'abuse'. Good quality care is based on humanist values. It is an action which promotes quality care and prevents abuse, while developing human relations. It implies particular attention to people's needs and takes professional practices into account.

With regard to the ill elderly, good quality care is expressed in two essential and complementary aspects: the quality of care and the quality of care giving. Quality of life is certainly the pursued objective.

Both at home and in a retirement home, good quality care implies several actions:

- Locate, evaluate and treat pain, which is not always easy when verbal expression is lacking.
- Diagnose depression while considering the risk of suicide.
- Maintain mobility, compensate for functional deficiencies.
- Prevent and treat malnutrition.
- End-of-life care and symptom relief.
- Provide, whatever the need, care quality and continuity, without abandoning technical aspects, while respecting the person's choice.

In retirement homes, the prevalence of dependence, multipathology and, in particular, cognitive disorders is 50–80% of residents; which gives these actions their great importance.

A reminder of the main ethical principles

In a preventive approach, we should recall fundamental ethical principles that must guide geriatricians in their daily practice of caring for vulnerable people:

- *Principle of humanity and dignity*. Everyone, whatever their condition, situation and personal history, has the quality of being human and therefore belongs to a community of human beings. It is a universal and inalienable principle.
- *Principle of solidarity*. People belonging to the same human community are bound by a collective responsibility to grant mutual aid and help to those afflicted by the misfortunes of life.

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• *Principle of fairness and justice*. This principle requires, for every person, the recognition and respect of their rights. Thus, age must not be a pretext to refuse access to diagnostic methods and/or to care, while appreciating, of course, the necessity to avoid relentless therapy.
• *Principle of autonomy*. This principle requires that each individual can freely rule their own life and make their own decisions concerning it.

Multidimensional aspects of abuse

Abuse expresses itself in various ways. The Council of Europe (1992) proposed the following classification. Abuse can be of various natures:
• Physical: blows, bodily cruelty, contention.
• Psychological: verbal violence, insults, familiarity, infantilization, threat of violence, deprivation of visits.
• Financial and material: theft or misappropriation of money, coerced signed cheques, anticipated inheritance.
• Medical: deprivation of medicine and care, lack of basic care, inappropriate care, no treatment information, neuroleptic abuse, no pain relief, lack of care coordination, and so on.
• Infringement of people's rights, their identity, their liberty to come and go, deprivation of the exercise of civic rights and the right to choose, religious practice, abusive use of legal protection.

However, it is necessary also to distinguish situations characterized by negligence:
• Active negligence corresponds to deprivation of indispensable daily care (eating, drinking, receiving visits, etc.), to defective aid leading to unacceptable hygiene, to abandonment, to putting the person in danger.
• Passive negligence results from forgetfulness: there is no intention to harm. It is a result of a lack of aid in getting up, putting to bed, grooming, dressing, walking, and so on. This attitude is a matter of ignorance and inattention to one's duty. Thus in retirement homes, the staff may be negligent because of a lack of training, a shortage in the workforce or ill-adapted working conditions.

The reality in the field teaches us that situations are often intricate, associating medical, psychological, social and economic issues, creating a complex scenario whose analysis proves difficult.

What are the clinical signs which lead us to suspect abuse? The presence of bruises, repetitive unexplained traumatic lesions, pelvic pains or genital bleeding, muteness or agitation on the part of the elderly person in front of a family or professional carer, malnutrition, deficient hygiene, regular trips to the emergency room of a neighbouring hospital, must draw professionals' attention. However, one needs to be careful of elderly people who say they are being abused but who, in fact, live in a delirium of persecution.

But who abuses?

Several situations involve some risk of progressing towards abuse. They must be known, in order to employ preventive measures, both at home and in care establishments. Thus, recent female widowhood, functional dependence, physical problems with urinary incontinence, psychological dependence and behavioural disorders (e.g. Alzheimer's disease) represent factors linked directly to the elderly person.

In the private sphere, the aggressor may be one or more family members, a neighbour, a 'friend'. They are often characterized by overt alcoholism, a difficult social and financial situation or a psychiatric illness. Ignorance of the illness, its non-acceptance, fear of dependence, exhaustion, isolation with a refusal of outside help, all aggravate the context.

The cohabitation of victim and aggressor in a small home facilitates abuse. In a care establishment, staff shortages, lack of trained teams, emotional exhaustion and professional attrition contribute to this failing. We therefore understand the importance of the establishment's project and the managing team's motivation, responsible for maintaining working conditions. However, ill-adapted premises and facilities and poorly used space present security risks for the residents and also represent a kind of abuse.

Conduct to embrace

Preventing abuse situations must be a priority in caring for elderly vulnerable people. It is the role of public authorities, associations and professionals that work in the geriatric field. This prevention calls for information, training and organizing effective measures.

In cases of abuse, either established or suspected, the priority is to protect the victim, in addition to taking into account the person's wishes. Often, hospitalization is the required solution, taking the person away from their presumed aggressor.

In other situations corresponding to suffering or exhaustion of care givers, it is necessary to break the isolation of the victim–aggressor couple, by the intervention of professionals at home, by temporary lodging, by protective legal measures, and so on.

French law stipulates that any qualified abuse offence must be brought to the judicial authority's attention (state prosecutor). The physician is no longer bound by professional confidentiality. Confirming abuse is a matter for penal jurisdiction.

Article 434-3 of the Penal Code

The Article states: 'The fact, for whoever having had knowledge of deprivations, abuse or sexual harassment inflicted on a minor under fifteen or a person who cannot protect

himself because of his age, an illness, an infirmity, a physical or psychological deficiency or pregnancy and not having informed the judicial or administrative authorities is punishable by up to 3 years' imprisonment and a 45 000 euro fine'.

Any complaint of abuse must be heard by trained and experienced people and must be discreetly investigated to confirm or invalidate its authenticity.

The laws

Several years ago, France created certain laws to promote good treatment and thus prevent abuse.

The democracy health law (2002) not only recognizes individual patients' rights, but also the collective rights of associations and their users: the right to respect and dignity, to care aimed at relieving pain, rejecting discrimination in access to prevention or care.

It is stipulated that 'anyone over 18 can designate a trustworthy individual, who will be consulted and receive the necessary information to make decisions on behalf of the person in the event that he, one day, becomes incapable of expressing his will. This designation must be made in writing; it revocable at any time'.

The Leonetti law (2005), relating to patients' rights at the end of life, specifies that 'anyone over 18 can write anticipated instructions in case this person should, one day, become incapable of expressing his will. These anticipated instructions indicate the relative end-of-life wishes of the person concerning the conditions of limiting or stopping treatment. They are revocable at any time. Provided that they have been established at least 3 years before the person lapses into a state of unconsciousness, the physician takes this into account before any decision is made concerning an investigation, intervention or treatment.

'The physician protects the dying person's dignity and assures the quality of his end of life'. Important progress has been made in respecting the autonomy of ill people in the sense of respecting their life choices.

The plan for developing good quality care and reinforcing the fight against abuse was launched in 2007 by the Ministry of Health. With 10 measures, this plan of action aims to develop a culture of good quality care in establishments and reinforce the fight against abuse. Created in the framework of this plan is the National Agency of Social and Medico-Social Evaluation, qualified by the Minister of the 'Quality Care Agency'.

Establishments are encouraged to implement a method of improving quality: self-evaluation of their practices, definition of objectives to improve them and external controls. Abuse prevention becomes an element in the quality approach.

This plan also oversees the diffusion of good professional practices, elaborated by the National Agency of Social and Medico-Social Evaluation, intended for staff members. It is also interested in the residents' living environment.

Further, reporting cases of abuse is encouraged, thanks to an SOS abuse hotline and an information campaign communicating the telephone number. The designation of an abuse 'telephone contact' in every French Department allows for the coordination of information from different public services. The number of inspections in establishments has doubled, with sanctions included.

The expertise of the National Committee of Vigilance against abuse is extended to the handicapped.

The 2007 law on structural reform of legal protection for adults (future protective mandate, limitation of tutelages for people medically acknowledged to be incapable of exercising their rights) takes part in the fight against financial abuses.

It is in the framework of these missions that the National Agency of Social and Medico-Social Evaluation elaborated and distributed several recommendations for good professional practices, which include:

- Good quality care: definition and references for its implementation.
- Establishment manager's mission and supervisory role in abuse prevention and treatment.
- The person's expectations and personalized project.
- Implementation of an adaptation strategy for the staff's use with regard to accompanied people.
- The medico-psycho-social accompaniment of people suffering from Alzheimer's disease or related disorders.

In 2008, the Ministry reinforced measures in favour of good quality care for the elderly and handicapped in establishments by increasing unplanned inspections in lodging establishments for dependent elderly persons and renewed support for the national hotline dedicated to the fight against abuse. Every year establishments are obliged to address an internal 'good quality care' evaluation questionnaire to public authorities, completed and viewed by the management team and the President of the Social Life Council. In the absence of a self-evaluation or manifest incoherence in filling in the questionnaire, a flash investigation is carried out in order to identify the problems met by the establishment.

Staff training in the techniques of personalized accompaniment is supported and prefects are solicited to organize departmental 'good quality care' meetings.

After a first report on these measures in favour of good quality care, the Minister declared, 'The culture of good quality care is a collective approach aiming to assure the best possible accompaniment for the elderly, at home or in an establishment, respecting their choices and adapting to their needs. Actions carried out in the framework of operating good quality care in establishments and the opening of a hotline number to fight against all forms of abuse concerning the elderly or handicapped prove that

good quality care is a functioning reality mobilizing professionals and public authorities in a voluntary and permanent way'. The social service hotline number received 63 858 calls between 5 February 2008 and 15 April 2009; 81% pertained to problems of abuse, 25.3% of which were psychological abuse; 80% of the controls carried out in medico-social establishments were unplanned verifications.

Finally, the training process of the establishments' staff has a good quality care approach and is engaged in the objective 'to train 100% of retirement home managers in a good quality care culture and organize training for the entire staff'. In 2010, the Minister reinforced the operation again, insisting especially on training intervening parties, professionals and family carers. For abuse predominantly occurring at home, he proposed, regarding family accompaniment, the concept of 'short training sessions' to 'help carers, preparing, enlightening and supporting them'.

Concerning care establishments, the evaluation of quality is reinforced. Some of them received a compliance request. Public authorities are very vigilant concerning formulated request applications (for example, the obligation for medicalization because of the dependent people concerned). Non-conforming establishments, within 3 months, run the risk of being closed down.

Other contributions

Indirect contributions of different public health plans include the pain management improvement plan, the quality of life of people presenting chronic affection plan, the Alzheimer's plan and the palliative care plan.

However, the mobilization of the High Health Authority reinforces the certification requirements of hospitals with the implementation of a complaint management system, the implementation of patients' end-of-life rights and the implementation of a promotional approach for good quality care.

This approach is based on an engagement on behalf of the management and establishment authorities, in particular from the Relations Commission with the Users and the Quality of Care to promote good quality care; training and professional awareness; abuse prevention actions; but also concrete and various actions centred on the daily experience of users, aiming to improve reception, efficient implementation of rights and meeting the needs of people.

MobiQual – mobilization for the improvement of the quality of professional practices

The objective of this national action, implemented by the French Society of Geriatrics and Gerontology, on the initiative of the Ministry of Health and supported by the National Solidarity for Autonomy Fund, is to improve professional practices in retirement homes, in health establishments and in private homes. This approach mobilizes all the actors concerned: public authorities, establishment and service federations, scholarly societies and voluntary service professionals, in the name of quality care and to take care of the elderly and handicapped. It rests on a common base, one of good quality care and specific themes: pain, depression, palliative care, end-of-life accompaniment, nutrition, Alzheimer's disease and risk of infection. It provides useful tools for all professionals: collective reflection guides helping institutional projects develop; professional training to strengthen theoretical and practical knowledge; help in decision-making and practice for quality and harmonious multidisciplinary practice; and cooperative link supports to strengthen the collective expertise. These tools are given to all voluntary establishments to use, in return for a charter attesting to their proper use.

This action includes an implementation and follow-up system: a national team project, guaranteeing the method of diffusion and integrating public authorities, references for each tool, establishment and service federations and a national coordinator for follow-up and evaluation.

The action therefore aims to make the staff aware of EHPAD (établissements d'hébergement pour personnes agées dépendantes), carers and non-carers, to a method of good quality care, while helping them to spot and prevent risky situations and proposing good quality care evaluation tools.

The approach consists of proposing voluntary EHPAD a good quality care kit, accompanied by awareness/training action intended for all professional actors intervening in EHPAD.

MobiQual

'What is good quality care on the institutional level, in the establishment where I work?'

- 'What is good quality care for me, who works in this establishment?'
- 'What is good quality care for the person living in the establishment where I work?'
- 'What is good quality care for the entourage of people living in the establishment where I work?'

> *Good quality care is an interrogation and must be reinvented, starting from some fundamentals, by each establishment and service.*
>
> National Agency of Social and Medico-Social Evaluation.

It is necessary to develop training, but also to give staff time to discuss and reflect. It is necessary to recognize and to evaluate the level of reflection of most carers, because one can only give good treatment if one is treated well.

A temporary report, written at the beginning of 2010, specifies that more than 9000 tools have been distributed to

establishments, corresponding to about 245 000 professionals concerned.

The objective the French Society of Geriatrics and Gerontology is to pursue and to develop the programme, in a period of 3 years, starting in 2010, thanks to financial support from the National Solidarity for Autonomy Fund, the Ministry's involvement and the mobilization of geriatricians in the regions.

Further comments

• In France, good quality care is henceforth at the heart of public policies and evaluation methods and improved practices in the socio-medical sector. This approach aims to compel organizations to be more considerate of the needs and expectations of people, to promote the person's wellbeing and keep in mind the risks of abuse.
• Progressively, these developments are also taking hold in the health and hospital fields.
• Coherent public policy on this good quality care theme is a major issue for the French Society of Geriatrics and Gerontology, which endeavours to carry its deliberations to the highest state level.
• Since 2007, some considerable progress has been made, providing an indisputable consistency to the following dynamic: from the priorities for training decreed by the Ministry, to recommendations by agencies, good quality care established as an indicator of quality for professional practices, but also for health and socio-medical establishments.

Conclusion

The mission of developing good quality care in health and socio-medical establishments is now entrusted to Regional Health Agencies, created by the Hospital, Patient, Health and Territories law (2009). It is a signal of transformation. Therefore, let us hope that the twenty-first century will be the one for rights of the elderly, like the twentieth century was for childrens' rights.

However, this aspiration will not fully materialize unless society progressively changes its outlook on the elderly and ageing.

Key points

- Medical and economic factors can contribute to vulnerable situations, which can lead to maltreatment.
- In a preventive approach, we should recall fundamental ethical principles that must guide geriatricians and other healthcare professionals in their daily practice of caring for vulnerable people.
- Preventing abuse situations must be a priority in caring for elderly vulnerable people. It is the role of public authorities, associations and professionals who work in the elderly care field.

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CHAPTER 120

Alcohol consumption and cognition

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Cognitive impairment is a public health concern for ageing adults. Some of the detrimental effects of heavy alcohol use on brain function are similar to those observed with Alzheimer's disease. Ethanol and acetaldehyde are toxins that negatively affect neural tissues and chronic heavy intake of ethanol is associated with an increased risk of alcohol-related central nervous system disease. Although the toxic effects of long-term, heavy alcohol intake on the central nervous system are well known, there is emerging evidence to suggest that moderate alcohol intake (one to three standard drinks per day) may be associated with a reduced risk of developing cognitive impairment.

Evidence from studies

In a cross-sectional population based study,[1] better global cognitive functioning assessed through psychometric tests such as the Mini Mental State Examination (MMSE) was associated with moderate wine consumption [odds ratio (OR) = 0.62; 95% confidence interval (CI), 0.48–0.81; $p = 0.0004$]. This association disappeared, however, when controlled for age, gender, educational level and occupational category, showing that confounding is a major issue in the study of alcohol consumption. Prospective studies also analysed the association between alcohol consumption and cognitive decline. A subsample of 387 survivors of 1083 subjects recruited between 1983 and 1985 in the cognitive substudy of the Medical Research Council treatment trial of hypertension was examined 9–12 years after the initial visit to assess cognition.[2] Poorer cognitive outcome was associated with abstinence from alcohol prior the age of 60 years.

In a randomly selected sample of 333 men living in Zutphen, The Netherlands, and followed for 8 years, low-to-moderate alcohol intake had a significantly lower risk for poor cognitive function (MMSE <25) than abstainers (OR of 0.3 for less than one drink and 0.2 for one to two drinks per day).[3] However, alcohol intake was not associated with cognitive decline. In women, alcohol consumption was also shown to be associated with a reduced risk of cognitive decline. Data from the Women's Health Initiative Memory Study of postmenopausal combination hormone therapy were used to assess cross-sectional and prospective associations of self-reported alcohol intake with cognitive function.[4] Compared with no intake, intake of ≥1 drink per day was associated with higher baseline modified MMSE scores ($p < 0.001$) and a covariate-adjusted OR of 0.40 (95% CI, 0.28–0.99) for significant decline in cognitive function over 3 years. Associations with incident probable dementia were of similar magnitude but were not statistically significant after covariate adjustment.

In the MoVIES project, cognitive functions and self-reported drinking habits were assessed at 2 year intervals over an average of 7 years of follow-up.[5] Trajectory analyses identified latent homogeneous groups with respect to frequency of alcohol use over time and their association with average decline over the same period in each cognitive domain. Three homogeneous trajectories were defined and were characterized as no drinking, minimal drinking and moderate drinking. Compared with no drinking, minimal drinking was associated with lesser decline on the MMSE (OR = 0.05; 95% CI, 0.01–0.26) and Trail Making Tests (OR = 0.02; 95% CI, 0.001–0.22), that evaluated executive functions. The same trends were observed for moderate drinking (MMSE, OR = 0.27; 95% CI, 0.09–0.84; Trail Making Test, OR = 0.15; 95% CI, 0.03–0.79). Minimal drinking was also associated with lesser decline in tests of learning and naming. These associations did not change on comparing current drinkers with former drinkers (quitters) and with lifelong abstainers.

Prospective evidence

The first prospective study to explore the association between alcohol intake and dementia was the PAQUID programme.[6] A sample of 3777 subjects aged 65 years or older was followed for 3 years and 99 incident cases of

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dementia were diagnosed. Alcohol consumption data were collected at baseline, with wine being the main type of alcohol consumed, usually on a daily basis. Four categories of individuals were defined: non-drinkers, mild drinkers (consuming up to 0.25 l of wine, i.e. two drinks per day), moderate drinkers (consuming up to 0.5 l of wine, i.e. three to four drinks per day) and heavy drinkers (consuming more than four drinks per day). Lower risks of developing dementia were found among drinkers compared with non-drinkers, but the relationship was significant only for moderate drinkers [mild drinkers, risk ratio (RR) = 0.81; moderate drinkers, RR = 0.19; heavy drinkers, RR = 0.31]. No modification effect was found according to gender and the association did not change after adjusting for age, gender, education, occupation and baseline cognition. After 10 years of follow-up, the association between baseline alcohol consumption and incident dementia remained significant, although the risk ratios tended to increase toward unity (mild drinkers, RR = 0.89, 95% CI, 0.70–1.15; moderate drinkers, RR = 0.56; 95% CI, 0.36–0.92).[7]

The Rotterdam Study followed 5395 subjects aged 55 years or older over a period of 6 years; 197 incidents cases of dementia were diagnosed.[8] The number of drinks of alcohol (beer, wine, fortified wine or spirits) was collected at baseline and five categories of intake were studied: no drinks consumed; less than one drink per week; more than one drink per week but less than one per day; one to three drinks per day; more than three drinks per day. The risk of developing dementia was lower among drinkers compared with non-drinkers (Table 120.1) and was significant in the 1–3 drinks per day category. The pattern was different in men and women. No association was found in women, whereas a lower risk was found for men drinking 1–3 drinks per day. A modification effect was found when the apolipoprotein E4 allele (ApoE4) was taken into consideration: the risk was lower among drinkers with an ApoE4 allele, whereas it was less clear for drinkers without the ApoE4 allele (Table 120.1). No difference was found according to beverage type, although beer tended to give marginally lower risk than wine.

In a prospective study of elderly people living in North Manhattan,[9] 2126 subjects were followed for 4 years and 260 incident cases of dementia were diagnosed. The number of drinks per week was collected at baseline and subjects were classified as non-drinkers, light drinkers (less than one drink per month to six drinks per week), moderate drinkers (one to three drinks per day) and heavy drinkers (more than three drinks per day). Light and moderate categories were aggregated because of the small number of moderate drinkers; in this sample, 70% of the subjects were non-drinkers. On analysing the association between each alcoholic beverage type and dementia, wine was significantly associated with a lower risk among light to moderate drinkers [hazard ratio (HR) = 0.64; $p = 0.018$]. On analysing the risk of Alzheimer's disease adjusted for age and gender, a decreased risk was observed in wine drinkers (HR = 0.59; $p = 0.018$), but the association became insignificant when education and the ApoE4 genotype (HR = 0.69; $p = 0.11$) were included. The risk ratios were >1 for light to moderate beer or spirits drinkers (beer, HR = 1.39; $p = 0.094$, spirits, HR = 1.34; $p = 0.152$). When wine, beer and spirits were analysed simultaneously with full adjustment, the risk for Alzheimer's disease was lower in wine drinkers (HR = 0.55; $p = 0.015$), but higher for beer (HR = 1.47; $p = 0.065$) or spirits (HR = 1.51; $p = 0.062$) drinkers. A modification effect was found with the ApoE4 genotype. A significantly lower risk of dementia was found in light to moderate wine drinkers without an ApoE4 allele (HR = 0.44; $p = 0.004$) compared with non-drinkers, whereas the association disappeared for ApoE4 allele bearers (HR = 1.10; $p = 0.093$). No modification effect by gender was found.

The association between alcohol intake and risk for dementia was also examined in studies originally designed to explore cardiovascular events. During follow-up, cognitive functioning was explored and nested case–control studies were performed. In the Copenhagen City Heart study,[10] a nested case–control included 83 cases of dementia and 1626 controls. Alcohol intake was collected in two ways: the number of drinks per week (<1, 1–7, 8–14, 15–21, 22 or more) and the frequency of intake (never/hardly ever, monthly, weekly, daily). No association was found between the number of drinks of alcohol consumed per week and the risk of dementia. When beer, wine and spirits intake were analysed simultaneously, a reduced risk was observed only for wine drinkers (monthly, HR = 0.43; 95%

Table 120.1 Hazard ratios (with 95% CI) of dementia according to alcohol consumption in the Rotterdam Study.

Group	No alcohol	<1 drink per week	≥1 drink per week but <1 per day	1–3 drinks per day	≥4 drinks per day
Total	1.00	0.82 (0.56–1.22)	0.75 (0.51–1.11)	0.58 (0.38–0.90)	1.0 (0.39–2.59)
Men	1.00	0.60 (0.27–1.34)	0.53 (0.28–1.0)	0.40 (0.21–0.74)	0.88 (0.32–2.44)
Women	1.00	0.91 (0.58–1.44)	0.91 (0.55–1.49)	0.85 (0.47–1.57)	–
ApoE4 absent	1.00	1.26 (0.67–2.37)	1.39 (0.73–2.64)	0.67 (0.31–1.46)	–
ApoE4 present	1.00	0.69 (0.35–1.34)	0.46 (0.23–0.94)	0.60 (0.30–1.21)	–

CI, 0.23–0.82; weekly, HR = 0.33; 95% CI, 0.13–0.86; daily, HR = 0.57; 95% CI, 0.15–2.11). Beer drinkers tended to have a higher risk (monthly, HR = 2.28; 95% CI, 1.13–4.60; weekly, HR = 2.15; 95% CI, 0.98–4.78; daily, HR = 1.73; 95% CI, 0.75–3.99) and no clear association was found in spirits drinkers (monthly, HR = 0.81; 95% CI, 0.42–1.57; weekly, HR = 1.65; 95% CI, 0.74–3.69; daily, HR = 1.12; 95% CI, 0.43–2.92). No difference was found between men and women.

Another nested case–control study was performed within the Cardiovascular Health Study, which included 373 cases of dementia and 373 controls.[11] Levels of alcohol intake were defined as 0, <1, 1–6, 7–13 and 14 or more drinks per week. The association between alcohol intake and the risk of dementia followed a J-shaped curve, with a nadir for the category of 1–6 drinks per week (Table 120.2). The pattern was different for men and women: all drinker categories were associated with a lower risk in women, whereas a J-shaped curve was found for men (Table 120.2). A modification effect by ApoE4 was observed: when the ApoE4 allele was absent, the risk was significantly lower among subjects who consumed 1–6 drinks per week. When the ApoE4 allele was present, the HR was below 1.00 only for light drinkers and above 1.00 for heavier drinkers (Table 120.2). The odds of dementia were lower (although not significantly) for wine drinkers (<1 drink per week, HR = 0.72; 95% CI, 0.46–1.11; 1–6 drinks per week, HR = 0.72; 95% CI, 0.39–1.33; >6 drinks per week, HR = 0.62; 95% CI, 0.25–1.50). However, the trend was not the same for beer (<1 drink per week, HR = 0.84; 95% CI, 0.48–1.47; 1–6 drinks per week, HR = 0.74; 95% CI, 0.36–1.54; >6 drinks per week, HR = 1.96; 95% CI, 0.71–5.4]) or spirits drinkers (<1 drink per week, HR = 0.84; 95% CI, 0.48–1.45; 1–6 drinks per week, HR = 1.17; 95% CI, 0.59–2.30; >6 drinks per week, HR = 1.08; 95% CI, 0.55–2.13).

Several other prospective studies have reported an association between alcohol consumption and dementia. A Canadian study[12] reported that at least weekly consumption of alcohol was associated with a decreased risk of Alzheimer's disease (OR = 0.68; 95% CI, 0.47–1.00). In Sweden,[13] the risk of dementia was estimated to be 0.5 (95% CI, 0.3–0.7) among light to moderate drinkers (1–21 drinks per week in men, 1–14 drinks per week in women). In China,[14] light to moderate drinkers (1–21 drinks per week in men, 1–14 drinks per week in women) had a lower risk (RR = 0.52; 95% CI, 0.32–0.85) than non-drinkers, but a non-significant increased risk was observed in heavy drinkers (RR = 1.45; 95% CI, 0.43–4.89). A greater reduction of risk was observed for men (RR = 0.37) than for women (RR = 0.76).

All these studies tend to show the same result: *light to moderate alcohol consumption is associated with a lower risk of developing dementia*. Which mechanisms may be involved in the risk reduction of dementia? One possibility is that alcohol might act by reducing cardiovascular risk factors, either through an inhibitory effect of ethanol on platelet aggregation or through alteration of the serum lipid profile. A second possibility is that alcohol might have a direct effect on cognition through the release of acetylcholine in the hippocampus. Finally, another possible mechanism is through the antioxidant activity of alcoholic beverages, particularly wine, which has been found to have important antioxidant effects.

However, the definition of light to moderate alcohol intake varies considerably across the studies reviewed. The classification of drinking as moderate ranges from monthly or weekly drinking to 3–4 drinks per day, and many studies reported an association for an intake of less than one drink per day. As alcohol intake is self-reported, it is also expected to be under-reported. However, neither a linear dose–response nor a J-shaped curve were systematically found over all studies and the association sometimes differed according to gender. The type of alcohol does not appear to be consistent across studies, yet wine intake is systematically associated with lower risk. If alcohol *per se* were associated with a decreased risk of developing dementia, the same pattern would be expected for beer and wine drinkers, yet beer has been found to be associated with higher risk in several studies.

Table 120.2 Odds (with 95% CI) of incident dementia according to alcohol consumption (drinks per week) in the Cardiovascular Health Study.

Group	None	<1	1–6	7–13	≥14
Total	1.00	0.65 (0.41–1.02)	0.46 (0.27–0.77)	0.69 (0.37–1.31)	1.22 (0.60–2.49)
Men	1.00	0.82 (0.38–1.78)	0.36 (0.17–0.77)	1.42 (0.58–3.48)	2.40 (0.86–6.64)
Women	1.00	0.52 (0.30–0.90)	0.57 (0.28–1.17)	0.23 (0.09–0.61)	0.39 (0.14–1.10)
ApoE4 absent	1.00	0.56 (0.33–0.97)	0.37 (0.20–0.67)	0.64 (0.30–1.38)	0.60 (0.24–1.51)
ApoE4 present	1.00	0.60 (0.24–1.52)	0.62 (0.21–1.81)	1.49 (0.33–6.65)	3.37 (0.67–17.1)

Conclusion

When analysing these results and discrepancies, one can wonder about the nature of the association between alcohol consumption and the risk of dementia. It can be hypothesized that alcohol intake (especially light to moderate intake) is only a marker of a broader psychosocial behaviour that is associated with a decreased risk of developing dementia. However, the analyses were controlled for many other risk factors and the association with alcohol was still significant. It is possible that important confounders (not yet identified) were not considered, which might explain some of the discrepancies between optimal intake, gender or type of alcohol. Light to moderate wine drinkers may prove to be moderate with regard to other risk factors of dementia and alcohol intake would only be an indicator of such behaviour.

Until such factors have been identified, we must be careful in how we interpret results relating to alcohol consumption. We have recently reanalysed the data of the PAQUID study with 20 years of follow-up. Among the 3676 non-demented subjects at the baseline screening, 830 developed dementia during the follow-up. After adjustment for age, gender and education, taking non-drinkers as the reference, the risk of dementia was lower in mild drinkers (HR = 0.85; 95% CI, 0.73–0.9), but failed to reach statistical significance for moderate drinkers (HR = 0.79; 95% CI, 0.60–1.04) and was neutral for heavy drinkers (HR = 1.01; 95% CI, 0.63–1.62). In the same cohort, during the 15 first years of follow-up, 2422 died. With the same adjustment and the same category of reference (non-drinkers), the risk of dying was weakly lower in mild drinkers but failed to reach statistical significance (HR = 0.94; 95% CI 0.86–1.03) and was neutral for moderate drinkers (HR = 1; 95% CI, 0.87–1.15) and for heavy drinkers (HR = 1.06; 95% CI, 0.83–1.36). That means that if a protective effect of mild wine consumption cannot be excluded, the impact of this effect was certainly weak and did not justify recommendations for prevention. People should not be encouraged to drink more in the belief that this will protect them against dementia. However, elderly people who drink mild to moderate amounts of alcohol have no clear reason to stop this little pleasure during ageing.

Key points

- There is emerging evidence to suggest that *moderate* alcohol intake (one to three standard drinks per day) may be associated with a reduced risk of developing cognitive impairment.
- In studies examining the relationship between alcohol intake and risk of dementia, when beer, wine and spirits intake were analysed simultaneously, a reduced risk was observed systematically for wine drinkers.
- There is evidence that among the apoE4 allele bearers, alcohol intake may reduce the risk of dementia in light drinkers compared with non-drinkers.

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CHAPTER 121

Drug misuse and the older person: a contradiction in terms?

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Introduction

There are two possible definitions of 'drug misuse'. The first, obvious, definition is 'drug abuse' with the term 'drug' used to cover illicit substances, but also non-compliant use of prescription drugs such as psychotropic medications and opioids. This drug abuse, which is not peculiar to older people, results from a complex interaction between a substance, a patient and its environment. However, older people are also exposed to another great danger: adverse drug reactions, with the term of 'drug' used to cover licit medication prescribed in agreement with basic medical rules. Here comes the second definition. Avoidable adverse drug reactions result from another interaction, as complex as the first one, involving a substance, a patient and its environment and the medical practitioner. For dementia, it could be even more complex, in part because of cognitive disorder, but also because of another factor that should be taken into account: the professional or informal stakeholder. For example, this one could ask for sedative medication prescription, not only for the direct patient benefit but also for their own quality of life. Both definitions have several meeting points, in particular for psychotropic medications: addiction, dependence, abstinence syndromes and health problems. In both definitions, it is, in most cases, an inappropriate response to a real issue. Consequently, to limit avoidable adverse drug reactions, we need to greatly change the way in which we prescribe for older people.

Drug abuse

For coverage on this subject, see Chapter 122, The use and abuse of prescribed medicines.

Medications and the elderly: geriatric characteristics, adverse drug reactions and drug misuse

Medications and the elderly: characteristics

Benefit–risk evaluation of medications in the elderly

The elderly and clinical trials

Phase III

When a medication has been shown to be effective in the young adult, it is also conventionally accepted that it is generally effective in the elderly. However, such an assertion can be discounted. For example, O'Hare *et al*.[1] carried out a literature review of the indications of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II-receptor antagonists (AIIRA) in chronic kidney disease in the elderly. They came to the conclusion that the recommendations were based on data that are not relevant to the elderly, because of differences in the causes of chronic kidney disease. Similarly, the SENIORS study, performed to determine the effect of nebivolol as add-on therapy in elderly patients with heart failure, regardless of ejection fraction,[2] found that, *a priori*, efficacy was lower than in the young adult.

Medication risks are very poorly evaluated before market authorization, for three essential reasons. First, non-inclusion in Phase III trials of subjects with several concomitant disorders and receiving several medications: very elderly persons are among the populations excluded from clinical trials, including trials that include patients over 65 years of age, if these subjects present comorbid conditions. Several years ago, attention was drawn to this point by international recommendations that have not yet been implemented. Second, inadequate

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collection of adverse effects is also a great limitation. Third, premarketing trials, although they can evaluate the efficacy of a medication in a controlled setting, only detect adverse drug reactions (ADRs) when these occur in more than one case in 100 and are not limited to a particular subgroup. This being so, they yield only relatively restricted information on safety of use (including in the young adult). The denominator of the benefit–risk balance in the elderly patient can only be known through information gained in Phase IV.

Phase IV

In the USA, over a 25 year period, 10% of new drugs were withdrawn from the market or were the subject of major alerts and half of the withdrawals occurred within 2 years of drug introduction.[3]

Through pharmacovigilance, Phase IV notably allows the collection of information on drug-related risk. However, spontaneous notification, which is the cornerstone of pharmacovigilance, principally yields information on type B adverse effects (bizarre or idiosyncratic effects, dose independent and unpredictable) and not on type A adverse effects (augmented pharmacological effects, dose dependent and predictable) which have the dual specificity of being more frequent and also of often being avoidable.

In practice

As the complete information needed to determine the benefit–risk ratio in elderly patients is not available and as the treatment decision cannot be based only on expected efficacy, guidelines with regard to this frail elderly population are often based on low levels of evidence, notably concerning insufficiency of treatment (see the section Classification of the various types of suboptimal prescription) and so affect the expected benefit–risk ratio.

Age and adverse drug reactions

Elderly persons may be more at risk of ADRs due to physiological age-related changes that influence the pharmacodynamics and pharmacokinetics of drugs.[4] These reactions are more frequent after the age of 65 years. However, once confounding factors have been taken into account, age does not seem to be an independent risk factor for ADRs[5] but it is a factor of gravity of such events.

Polypharmacy and adverse drug reactions

Polymorbidity leads to polypharmacy, which may be expected to yield certain benefits. However, polypharmacy, because of disease–disease and drug–disease interactions, may in fact decrease the benefit–risk balance of the treatments given. There are two possible definitions of polypharmacy.[6] The first is concomitant use of several medications. However, although some investigators used a threshold of 3–5 medications, no exact figure has been clearly established. A second definition is overuse or use of more medications than is clinically necessary (see the section Classification of the various types of suboptimal prescription). This definition carries the negative connotation of suboptimal prescription, but without fixing an arbitrary threshold.

Polypharmacy (in the sense of the total number of medications taken) is an independent risk factor of iatrogenic events that is constantly found in the literature. In a study by Gallagher and O'Mahoney, patients taking more than five medications were at greater risk of hospital admission because of inappropriate prescription.[7] Mackinnon and Hepler developed a set of indicators of avoidable ADR[8] and applied it retrospectively to a hospital database.[9] One of the main risk factors was found to be the number of medications (>5). A recent review of the literature showed that polypharmacy is increasing and is a risk factor for morbidity and mortality.[10] The use of an arbitrary number as a cut-off is, however debatable. Viktil *et al*.[11] carried out a hospital-based multicentre prospective study of 827 patients, aiming to determine whether polypharmacy defined as a given number of drugs is a suitable indicator for describing the risk of ADRs. The number of ADRs per patient increased in an almost linear manner with the number of medications at admission. One unit increase in number of drugs increased the incidence of ADRs by 8.6% [95% confidence interval (CI), 1.07–1.10]. The most appropriate definition of polypharmacy in geriatrics therefore seems to be the accumulation of medications considered useless and/or likely to lead to drug interferences.

Several studies found an association between the number of medications and use of inappropriate medications,[12] including an important retrospective study of 2707 elderly patients receiving home care in eight European countries.[13]

Disease–drug interactions, risk factors for iatrogenic events

In this section, we will not address 'classic' disease–drug interactions, such as chronic obstructive pulmonary disease (COPD) and beta-blockers, which are not specific to geriatrics.

Some elderly persons are at increased risk of iatrogenic events. Some authors[14] suggest that the following comorbid conditions should be considered as increasing the risk of ADR: frailty, renal insufficiency and cognitive impairment. As the incidence of ADRs is higher in women, female gender is a potential iatrogenic risk factor. In the study of Gallagher and O'Mahoney, for example, women were twice as likely as men to be admitted to hospital due to inappropriate prescription.[7] With regard to comorbid conditions, an Australian cohort study found that cardiac failure, chronic pulmonary disease, diabetes, renal or liver failure, rheumatological disease and cancers were associated with greater

risk of repeated admissions for ADRs.[15] Mackinnon and Hepler, in their retrospective study,[9] found that the number of comorbid conditions was among the main risk factors for avoidable ADRs.

With regard to cognitive impairment, publications are sparse. In a prospective study of patients with Alzheimer's disease, medications were a contributory factor to admission in 25% of cases.[16] In another French cohort[17] of 80 patients with dementia, 37% of short-stay hospital admissions were secondary to an ADR and 57% of admissions were due to potentially avoidable ADRs. About 20% of the ADRs observed were falls and the medications most often involved were psychotropic agents. There appears to be an excess risk of iatrogenic events in persons with dementia. The extent of avoidable iatrogenic events and inappropriate prescriptions is still very poorly known in this population.

Drug–drug interactions

Use of several medications and more numerous comorbid conditions are associated with increased risk of a potential interaction.

Drug interactions in the elderly patient fall into three main categories.[18] Conventionally, these involve drugs with a narrow therapeutic window such as digoxin, phenytoin and warfarin. These interactions are often well known, monitoring tests are available and they are detected by all prescribing software programs. The second category concerns complex interactions; patients with nine medications or more or with numerous comorbid conditions are often in this category. The choice of each medication in isolation is generally appropriate. The third category is the prescribing cascade: an ADR is interpreted as a new independent disease state for which another medication is prescribed and the patient is then susceptible to present with other ADRs because of this unnecessary medication. We can cite, as an example, patients receiving cholinesterase inhibitors who are more at risk of receiving an anticholinergic drug for new-onset incontinence.

A Swedish study of the elderly population showed an increase in polypharmacy and potentially clinically significant interactions between 1992 and 2002.[19] The proportion of elderly persons exposed to potentially clinically significant interactions rose from 17 to 25% in the 10 year period.

Clinical manifestations of drug interactions

A French study[20] analysed for one year the medications taken by elderly patients admitted to a geriatric unit: of the 894 patients (89.4%) who took at least two medications, 538 (60.2%) were exposed to 1087 potential interactions. Clinical or biological effects were observed in 130 patients (14.5% of patients taking two or more medications). A review of the literature from 1990 to 2006 relating to drug interactions in the general population suggests that although potential drug interactions are frequent, they rarely lead to hospital admission. However, this rate seems to increase with age, rising from 0.57 to 4.8% of admissions of elderly patients.[21] Juurlink *et al*.[22] carried out a 7 year case–control study of all patients aged 66 years or over living in Ontario, Canada, and treated with glyburide, digoxin or ACE inhibitors. In the week before admission, patients receiving glyburide and admitted for hypoglycaemia were six times more likely to have taken cotrimoxazole, patients receiving digoxin admitted for ADR were 12 times more likely to have been treated with clarithromycin and patients receiving ACE inhibitors and admitted for hyperkalaemia were 20 times more likely to have been treated with a potassium-sparing diuretic.

In practice

It is not realistic to think that physicians know and recognize all drug interactions. Prescribing software programs can help to reduce interactions but they raise the problem of numerous irrelevant alerts that are ultimately ignored by the prescriber, of significant but unrecognized interactions and updates that are not carried out. The problem is made more complex by the fact that it is difficult to know, among the potential interactions, which ones will be have a clinical expression. It therefore seems necessary to concentrate on monitoring the medications with a narrow therapeutic window, to look for potential interactions when a new comedication is introduced and to consider the possibility of an ADR when in the presence of symptoms of recent onset, in order to avoid the prescribing cascade.

Medications and the elderly: iatrogenic consequences

A large prospective study[23] showed, in a population that was not specifically geriatric, a 6.5% prevalence of hospital admissions secondary to an ADR. The drugs most often implicated were low-dose aspirin, diuretics (27%), warfarin and non-steroidal anti-inflammatory drugs (NSAIDs). The most common reaction was gastrointestinal bleeding, which was responsible for half of the deaths due to ADRs. These results, however, have to be adjusted for the consumption rates of these drugs. The mean age of subjects admitted for ADRs was 76 years (compared with 66 years for all admissions). Of these ADRs, 72% were considered to be avoidable.

The rate of ADR-related hospitalization appears higher in elderly than in younger adults. A meta-analysis of 17 observational studies estimated the mean rate of ADR-related admissions in elderly subjects as 16.6%.[24] A considerable proportion of these were judged to be avoidable. A cohort study of 30 397 persons followed for 1 year in an ambulatory setting found an overall rate of ADRs of 50 per 1000 patient-years, of which 27.6% were considered to be avoidable.[25] More than one-third of these ADRs (38%) were

judged to be severe, life-threatening or fatal and a higher proportion (42.2%) were avoidable. In an institutional setting, the incidence of ADRs varied according to the method of identification used, ranging from 1.19 ADRs for 100 patient-months to 7.26 ADRs for 100 patient-months with a computerized detection system.[26] Between 10 and 45% of the ADRs were considered severe.

Finally, ADRs are a frequent, or even the most frequent, cause of hospital admissions in the elderly. One-third to half of these reactions are severe and on average half could have been avoided.

Medications and the elderly: drug misuse or suboptimal prescribing

Classification of the various types of suboptimal prescription

The appropriateness of prescription reflects its quality. Terms such as optimal or suboptimal may also be used. Several types of suboptimal prescription in elderly subjects are classically described: excess treatment (overuse), inappropriate prescription (misuse) and insufficient treatment (underuse).[6] The indicators defined in Anglo-Saxon countries for assessing prescription quality for the elderly generally employ these three types. To sum up, for a given patient, certain treatments can be considered inappropriate and others insufficiently prescribed. Although it is legitimate in a quantitative approach to seek to reduce the number of medications taken by a patient, close qualitative analysis cannot be dispensed with. For this reason, the number of medications is not a good judgement criterion.

Excess treatment or overuse

This concerns the use of medications prescribed in the absence of an indication (the indication has never existed or no longer exists) or prescription of medications whose efficacy is not proven (insufficient medical service rendered).

Inappropriate prescription or misuse

This relates to use of medications whose risks exceed the expected benefits. This concept was first introduced by Beers, who established a list of drugs to avoid. The list has since been adapted for ambulatory patients and updated.[27]

Insufficient treatment or underuse

This is defined as the absence of initiation of an effective treatment in subjects with a condition for which one or several drug classes have demonstrated their efficacy.

As the frail elderly are generally excluded from clinical trials, a drug–indication pair must fulfil several conditions in order to comply with the definition of underuse:

- It must have a benefit–risk balance that is unquestionably favourable in a population of robust younger adults.
- This benefit, observed in a robust subject, should *a priori* be found in an elderly subject.
- It must not present major excess risk in the frail elderly population (which means that safety data on its use after marketing authorization need to be available).
- It should, to some extent, have been the object of clinical studies revealing increased overall mortality in undertreated patients, but these are observational data that are generally biased.

Four risks can easily be identified:

1 Risk of being satisfied with a debatable diagnosis. Some authors speak of 'underuse' abusively, for example in basing the indication of antidepressant treatment on administration of the short version of the Geriatric Depression Scale. Insufficiency of prescription is related to the quality of the diagnostic investigations which may not have been carried out because of an at-risk comorbid condition.

2 Risk of not taking into account the potential contraindications to the treatment or any other well-founded decision not to treat, such as refusal by the patient.

3 In the absence of relevant clinical trials, the risk of being satisfied with a mediocre level of proof. An example is hormone replacement therapy in the indication of treating cognitive disturbances (on the basis of observational data).

4 The risk of basing treatment indication on data from clinical trials in robust subjects and so concerned only with potential benefit and not risk. An example is hypertensive treatment, which was cited as underprescribed treatment at a time when data on the benefit–risk balance were not available. Robust elderly subjects, finally, are not geriatric subjects.

Relations between the different types of suboptimal prescription (Figure 121.1)

A medication may be underprescribed, for example antidepressants in atypical depression of the elderly person, and at the same time could raise the problem of inappropriate prescription, such as when antidepressants are prescribed for life after an episode of reactive depression.

A study by Steinman *et al*.[28] found a constant rate of underuse whatever the total number of medications

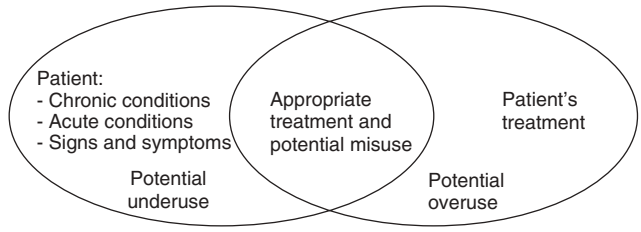

Figure 121.1 Different types of suboptimal prescription.

taken. Polypharmacy carries the risk of an increase in inappropriate prescriptions, while it does not restrict underuse. One possible interpretation of these findings is that polypharmacy is not a protection against underuse and that it is pertinent to restrict the number of medications to those which are strictly necessary by ranking the indications in order of importance.

What is the quality of prescription in the elderly when evaluated according to the different types of suboptimal prescription?

Overuse and inappropriate prescriptions

Examples of inappropriate prescriptions in the elderly are many. Among them are proton pump inhibitors (PPIs) prescribed for banal upper gastrointestinal symptoms or unduly prolonged after gastric ulcers. We may also cite overprescription of digoxin, notably in subjects living in institutions, which are responsible for a large number of serious adverse reactions, and some prescriptions of neuroleptics in nursing homes. Benzodiazepines are also prescribed in excess for insomnia or for anxiety which masks an unrecognized depressive syndrome. In the Three-City study, representative of the population aged 65 years and over living at home, 21.7% of elderly subjects were receiving an inappropriate medication:[12] 5.4% were taking dextropropoxyphen, 6.4% an anticholinergic medication and 9.2% benzodiazepines with a long half-life (more than 20 h). Studies assessing the rate of inappropriate prescriptions in Europe, as defined by the lists of Beers or McLeod, found rates ranging from 10 to 20%. [13,29] In nursing homes, the rate of inappropriate prescriptions is much higher and may be related to the risk of hospitalization and death.[30] A French prospective study carried out in a geriatric short-stay unit[14] showed that 66% of patients had at least one inappropriate medication at admission. Cerebral vasodilators were the most common, followed by long half-life benzodiazepines, dextropropoxyphen, anticholinergic antidepressants and the use of two or more psychotropic drugs of the same class.

Insufficient prescription

Numerous disorders may be undertreated in the elderly, bearing in mind all the limitations that we discussed in the preceding sections. The main disorders cited are systolic arterial hypertension above 160 mmHg, coronary insufficiency with underprescription of platelet anti-aggregants and beta-blockers, cardiac failure with systolic dysfunction and underprescription of ACE inhibitors,[31,32] atrial fibrillation with underprescription of AVK,[33] depression with underprescription of antidepressants and osteoporosis with fractures with underprescription of calcium, vitamin D and bisphosphonates. The authors of the evaluation tool for underuse START (see the section Analysis of available tools for evaluation of prescription quality)[34] applied their screening tool in a population of 600 patients aged over 65 years hospitalized for an acute medical problem : at least one potentially useful medication had been omitted in 57.9% of patients, in the absence of any contraindication. This rate reached 72.2% in patients aged over 85 years and women were twice as much at risk as men. The medications omitted mainly concerned cardiovascular disorders: statins in atherosclerotic disorders (26%), vitamin K antagonists in atrial fibrillation (9.5%), platelet anti-aggregants in arterial disease (7.3%), but also vitamin and calcium supplementation in osteoporosis with fractures (6%).

One study has shown that restricting access to certain medications for Medicaid patients in the USA more than doubled their rate of admission to an institution.[35] For certain medications, inadequate prescription could be associated with clinical criteria such as excess morbidity or mortality. We may also cite beta-blockers and ACE inhibitors.

Studies carried out on beneficiaries of the Medicare system throughout the USA examined the quality of the care received by these patients.[36] Of the 22 indicators of quality of care applied on a national level, nine concerned underuse. It was demonstrated, at a 2 year interval, that there was room for improvement in the prescription of essential medications such as beta-blockers and platelet anti-aggregants after myocardial infarction.[37]

Medication and the elderly: influence of suboptimal prescription in iatrogenic events in the elderly

Inappropriate medications versus inappropriate prescriptions

Some studies did not reveal an increase in ADRs associated with the medications on the Beers list.[14] Other authors concluded that these medications are responsible for only a small proportion of ADRs.[38] A longitudinal Swedish cohort (1995–98) of 785 patients aged over 75 years showed an excess risk (after adjustment for confounding factors) of at least one hospital admission with an odds ratio (OR) of 2.72 (95% CI, 1.64–4.51) in patients with inappropriate medications at baseline (according to a modified list of Beers criteria and evaluation of potential interactions in particular). No association was found with mortality.[39] In nursing homes, the rate of inappropriate prescriptions is high and appears to be linked with the risk of hospitalization and death.[30] An Irish study has also shown that 12% of hospital admissions were secondary to ADRs related to inappropriate prescriptions named on the STOPP list and 6% were related to medications named on the Beers list.[7] In a study by Budnitz *et al.*,[38] 3.6% of emergency admissions of elderly patients after an ADR were due to medications considered to be always inappropriate according to the Beers criteria, 5.2% to medications potentially inappropriate in

certain conditions, and 33.3% followed the use of three other medications: warfarin (17.3%), insulin (13%) and digoxin (3.2%). When frequency of prescription of these medications was taken into account, the risk of emergency hospitalization after their use was 35 times greater than the risk related to use of medications considered as always inappropriate. A limitation of Budnitz *et al.*' study is the fact that laboratory tests make attribution of imputability easier with AVK, insulin, diuretics or digoxin in particular, whereas the imputability of psychotropic agents, for example, is generally less simple. A study by Pirmohamed *et al.*,[23] even though it did not specifically concern a geriatric population, found similar results with the following medications being most commonly implicated: low-dose aspirin, diuretics, warfarin and NSAIDs, which are not considered inappropriate in the elderly.

In an ambulatory cohort of 30 397 persons followed for 1 year,[25] the majority of errors associated with avoidable ADRs occurred at the monitoring stage (60.8%) before prescription (58.4%). Cardiovascular medications (24.5%), diuretics (22.1%), non-opiate analgesics (15.4%), hypoglycaemic agents (10.9%) and anticoagulants (10.2%) were most often implicated. In an institutional setting,[26] the majority of errors also occurred at the monitoring stage (70–80%) before prescription (60–70%).

It seems more relevant to encourage good prescribing practices with the aim of reducing avoidable iatrogenic events than to stigmatize inappropriate treatments. These events appear to be due above all to defective monitoring rather than to an inopportune choice of medication. The association between inappropriate medications and undesirable events is no longer open to doubt,[30] but the importance of their role in iatrogenic events in the elderly is debated.

Clinical efficacy of interventions for treatment optimization

Few studies of treatment optimization have shown their efficacy in improving clinical criteria. In 2007, Spinewine *et al.*[30] reviewed the literature on inappropriate prescriptions in the elderly. Of 14 interventional studies, two showed an improvement in clinical criteria such as reduction of severe ADRs or better pain control and fewer hospital admissions. The authors of one study obtained improvements in the Medication Appropriateness Index score (MAI) in two studies and decreased hospital usage in one of them and some others a reduction in the number of falls. In some cases, withdrawal of medications judged not indispensable in the elderly person can have secondary benefits such as a reduction in falls and improvement of cognitive disturbance when a psychotropic agent is discontinued.

This type of study appears to have several evident limitations, in particular because of the focus on medications termed inappropriate and not on the quality of prescription. In addition, identifying at-risk situations by observation is very different from preventing them before they occur.

Prevention of iatrogenic incidents in practice: general rules for individual prescription

Risks are related to the medications themselves, but above all to the way in which they are used. This point is dealt with in extensively the section Inappropriate medications versus inappropriate prescriptions. Application of the general rules of prescription in the elderly person is of major importance in order to limit avoidable iatrogenic events.

Taking the conventional definition of non-optimal prescriptions in the elderly person and extending it, we can propose a broader definition of optimal treatment. It is a question of adapting, taking into account the present state of scientific knowledge, the patient's treatment for his or her disorders in the wider sense of the term:

- chronic conditions (such as dementia, COPD)
- acute conditions requiring overall reassessment of treatment (such as dehydration, falls, confusion)
- signs and symptoms (such as pain, constipation)
- overall gerontological evaluation (such as cognitive function, risk of falls, autonomy),

while ensuring at the same time treatment follow-up according to pre-established criteria of efficacy and risk. Obviously, this is a dynamic process which does not end with the initial act of prescription.

Starting treatment

Diagnostic stage

The first phase of prescription is diagnosis. In a frail geriatric population, the physician sometimes hesitates to carry out the appropriate investigations. However, the risk may be less than that of exposing the patient to blind treatment which will probably not be of any benefit. In these situations of uncertainty, we can sometimes see a tendency to treat with medications that render low medical service but that have the reputation of being well tolerated, rather than by first-line treatments. However, as the benefit gained is generally nil, the risk incurred is not tolerable.

Evaluation of benefit

Once the diagnosis has been made, the potential benefit of the treatment must be determined according to the precise context: reduction of morbidity and mortality, improved comfort and so on. The opinion of the patient and their caregiver must be sought. For example, a high proportion of patients do not know they are receiving antidepressants.

The choice must obviously go to first-line treatments with a maximum level of proof in the robust subject.

Evaluation of risk

As we are dealing with a non-ideal population that is at risk of iatrogenic events, the second stage is to identify at-risk subpopulations. The decision not to treat may be made because of:

- interactions with essential medications (such as NSAIDs associated with ACE inhibitors)
- interactions with comorbid conditions (such as AChE inhibitors and severe COPD)
- an at-risk context (such as digoxin in a demented patient living at home)
- disagreement of the patient or their caregiver because of the potential risks.

If the decision to treat is made, it is necessary to assess drug–drug and drug–disease interactions. Some patients are receiving inappropriate doses of renally excreted drugs and inadequate dose adjustment, in particular for renal function, is the cause of a considerable number of ADRs.

Lastly, scheduling treatment over time is part of the initiation stage. Information on the starting date of an antidepressant treatment is generally not found. Discontinuation must also be scheduled, both in the medical record and with the patient, right from the time the treatment is introduced. For hypnotic agents, benzodiazepines in particular, as soon as treatment is started it is necessary to schedule its discontinuation in conjunction with the patient.

It is noteworthy that one of the main avoidable risk factors of ADRs is the number of prescribing physicians.[9]

Treatment follow-up, adverse drug reaction alert

Time schedule

Treatment follow-up requires that a time schedule should have been determined as soon as treatment was started: start date and end date (e.g. PPI, antidepressants), date for evaluation of efficacy (e.g. antidepressant at 4–6 weeks) and date of safety evaluation (e.g. ACE inhibitors and serum creatinine at 10 days).

Tools for monitoring treatment efficacy

To monitor treatment efficacy, the target indicators must have been identified: clinical criteria (DSM-IV target criteria in depression, for example), biological criteria (serum digoxin, INR) and also target criteria for safety. If treatment fails, compliance should always be checked (beware of escalation of antihypertensive drugs).

Tools for risk prevention and control

As we have seen, treatment follow-up is the cornerstone of prevention of iatrogenic events. At-risk situations can be identified by target indicators of safety or adverse drug reaction alerts. These indicators may be patient dependent, in which case they require identification of at-risk populations (see the section Disease–drug interactions, risk factors for iatrogenic events): women, elderly patients with several comorbid conditions, renal failure, dementia or malnutrition and also patients at risk of falls. The indicators may be dependent on drug-related factors: polypharmacy, medications with a narrow therapeutic window (such as AVK, diuretics, digoxin), psychotropic or cardiovascular drugs, newly marketed drugs. Lastly, they may be dependent on intercurrent events, such as water and salt depletion or introduction or discontinuation of a medication. The role of intercurrent events is particularly important, whether introduction or discontinuation of a medication that is a source of drug interactions or the onset of an additional acute condition (such as diarrhoea, vomiting and dehydration) or variations in climate.

The authors of a retrospective Italian study[40] analysed the records of 16 037 patients (mean age 53.1 years). With regard to monitoring, 28% of patients who had been taking both digoxin and diuretics for at least 5 months had had no control tests and only 11% had had an ECG and serum digoxin and also potassium measurement. Of patients who had been receiving digoxin and amiodarone/verapamil/propafenone for at least 5 months, 36% had had no test. In France, a study by the national health insurance organisation (Caisse Nationale de l'Assurance Maladie) showed that 22.8% of patients aged over 75 years taking diuretics for 12 months had had no laboratory tests during this time. With regard to drug-related factors, the patients who had received the least monitoring were those receiving a fixed diuretics combination.

Global re-evaluation of treatment

Finally, the entire treatment must be reassessed: this must be done when there is an intercurrent event and when a new drug is introduced, and also systematically, for instance once per year (Table 121.1). Periodical review of treatment, for example by a clinical pharmacist or a multidisciplinary team, seems to reduce inappropriate treatments.

Treatment discontinuation

When a medication is not or is no longer indicated, withdrawal rarely seems to be a problem. However, caution is still needed in some situations: beta-blockers and coronary insufficiency, long-term high-dose benzodiazepines and insomnia, corticosteroids and Horton's disease, antiepileptic drugs and epilepsy, anti-Parkinson drugs and Parkinson's disease and so on. More anecdotal is the potential treatment imbalance when an enzyme inducer or inhibitor is discontinued or during changeover between two drugs with a risk of interaction (e.g. the interval of 15 days between discontinuation of a MAOI and starting an SRI). Withdrawal is easier when full information was given when the drug was started, for benzodiazepines for example.

Table 121.1 Example of monitoring criteria for treatment follow-up.

Indication	Drug name	Introduction date	Posology	Duration	Monitoring criteria	
					Efficacy	Security
Heart failure	Enalapril	yyyy/mm/dd	mg per day	Lifetime	Dyspnoea	Kalaemia Serum creatinine Orthostatic hypotension

In some cases, discontinuation of medications considered as not absolutely necessary in the elderly person can be done without major risk – as in withdrawal of an antihypertensive agent which is no longer indispensable – and it may even have secondary benefits, such as a reduction in falls and improved cognition after a psychotropic agent is withdrawn.

Prevention of iatrogenic incidents in practice: tools for collective evaluation

General considerations

Concerning collective evaluation, with regard to prescription quality in the elderly, the potential avoidable ADR to be targeted must correspond to an explicit definition;[8] for example, the adverse event must have been foreseeable, its pre-existing drug-related origin must be identifiable from the information available (the patient's medical record) and the event must be preventable by changing the drug treatment. They also should:

- be well referenced
- be common in the population considered
- have a moderate to severe effect.

It also seems essential that these tools refer to the conventional modalities of non-optimal prescription, whose implication in avoidable iatrogenic events is no longer in doubt, and should include general prescribing rules which are of more importance in avoiding such events.

These evaluation tools are potentially useful to assess prescription quality at a collective level, but some of them could also be useful at an individual level.

Analysis of available tools for evaluation of prescription quality

Classic evaluation tools

Beers

The first to consider the concept of misuse was Beers, who established a list of medications to be avoided in the institutionalized elderly after carrying out a literature review and applying the Delphi method. The list has since been adapted for ambulatory patients and updated.[27] It is a tool which is more suitable for collective than individual evaluation. A revised French version of the list has been developed for application in the cohort of elderly subjects followed in the Three-City (3C) study.[12] The 1997 list was revised by a panel of experts in order to take French characteristics specifically into account.

IPET

Similar initiatives have been undertaken in Canada with the development, by a panel of experts, of a list of indicators divided into three categories: medications generally contraindicated in the elderly, drug–disease interactions and drug–drug interactions. An alternative is proposed for each indicator. This list has been adapted and evaluated by Naugler *et al*. to develop the Improving Prescribing in the Elderly Tool (IPET).[41]

START

This list of 22 clinical indicators, developed by Irish geriatricians, links a clinical situation with an appropriate prescription.[34] This tool, which can detect prescribing omissions, was validated using the Delphi method 'on the basis of the most recent evidence'. However, the studies which served as a basis for this list are not cited. The authors applied their screening tool to a population of 600 patients aged over 65 years hospitalized for an acute condition. In the absence of a contraindication, at least one potentially useful medication had been omitted in 57.9% of patients. This rate reached 72.2% in patients aged over 85 years and the risk was twice as great in women than in men.

STOPP

The authors developed a list of 65 criteria, aiming to identify potentially inappropriate prescriptions, through use of the Delphi method.[7] These criteria are intended to take different clinical situations into account better than the Beers list, for example in the prescription of tricyclic antidepressants (sometimes indicated at a low dose in neuropathic pain). Secondarily, they examined the performances of the STOPP tool compared with the updated Beers list[27] of 68 criteria, for detection of potentially inappropriate prescriptions and their associated ADRs in 715 elderly patients admitted to acute care units. The ADRs that contributed, directly or indirectly, to the reason for admission were identified subjectively (not by application of an algorithm

of imputability). An ADR was identified in this way in 90 patients (12.5%), of which 91% were identified by STOPP and 48% by Beers. The inappropriate prescriptions detected by STOPP contributed to 11.5% of admissions, compared with 6% for Beers. According to the authors, these results are in favour of the use of STOPP at an individual level to identify potential ADRs when the clinical presentation is non-specific such as falls or delirium, and they also act as a reminder to bear constantly in mind the possibility of a drug-related origin. With regard to the feasibility of using START, the investigators applied the grid in less than 3 min, once the list of the various conditions and treatments had been established.

Other tools

Mackinnon and Hepler in the USA developed a set of indicators of avoidable ADR using the Delphi method.[8] Their work has the advantage of being based on a clear definition of avoidable ADRs. The participants considered a clinical scenario as an indicator only if it first corresponded to the definition of an avoidable ADR. This explicit definition of avoidability consists of four points: for an undesirable event, a possible pre-existing drug-related origin must be (1) *recognizable*, the undesirable event or treatment failure must have been (2) *foreseeable* and the causes of the drug-related problem and the causes of the event must have been (3) *identifiable* and (4) *controllable*. The experts were therefore asked to respond to these four questions for each clinical scenario:

- In the majority of patients, should health professionals be capable of *identifying* a problem in therapeutic management?
- Should they be capable of *foreseeing* the possibility of this event if the problem is not solved?
- Should they be capable of seeing how management could be changed in order to *prevent* this event?
- Should they modify their management?

This list has the major advantage of including the three conventional types of suboptimal prescription, and also treatment monitoring. The authors retrospectively applied their set of indicators in order to determine the incidence of avoidable ADRs and to identify risk factors.[9] They found an incidence of 28.8 per 1000 avoidable ADRs with the principal risk factors being number of comorbid conditions, number of prescribers and number of medications (>5). These indicators, initially developed in the USA, were secondarily adapted to Canadian practice.

Other authors have established a list of 'positive' medications in geriatrics, restricted to medications with high medical service rendered, of which the prescriber could make better use in order to limit iatrogenic events. Such a list could be of service at a time when, in some European countries, care homes for the dependent elderly are called upon to set up their own internal pharmacy and so to make a choice of medications for priority use.

Limitations

The Beers list has been criticized:

- Concerning its relevance at an individual level. However, Beers and his co-workers never proposed that this list should be applied to individuals.
- Because it does not sum up all cases of inappropriate prescription and in particular does not take account of underuse.
- Because it includes certain medications such as nitrofurantoin or amiodarone,[7] whatever the situation in which they are used.
- Because few studies have reported a clinical benefit resulting from use of these criteria.[30]

These limitations also concern in part the other lists.

The major differences between the American and Canadian lists also raise a problem, as few of the criteria overlap. In a European study using a combination of the criteria of Beers and McLeod, about half the medications were not available in the majority of European countries.[13] Practice indicators need to be adapted to local conditions. For example, some indicators that are relevant in the USA may not be so in the UK because of differences in clinical practices. On the other hand, they can serve as a starting point for developing a more appropriate set, for example using the Delphi method.

We have already discussed the low correlation found between these scores and clinical criteria. We may also add that it is a very different matter to identify at-risk situations by observation and to prevent them beforehand.

Global evaluations tools

The previous lists have been criticized because they do not take into account all cases of inappropriate prescription and they only refer to treatment and not to general prescription rules, monitoring and so on. Some authors have tried to develop more comprehensive tools to assess prescription quality.

MAI

The Medication Appropriateness Index (MAI)[42] offers a more global evaluation of pharmacological management. The MAI incorporates explicit criteria and makes use of implicit instructions. Ten criteria are evaluated for each medication:

1 indication
2 efficacy
3 dosage
4 correct mode of administration
5 practical mode of administration
6 drug interactions
7 interactions with comorbid conditions

8 overlapping medications
9 duration
10 cost (e.g. the existence of an equivalent drug at least 25% less costly).

Each criterion can be weighted with a score of 0–18 per medication, giving a summated quality score. The MAI has been used in certain interventions for treatment optimization.[30] It gives a more global evaluation of the prescription but does not assess all modalities of non-optimal prescription, in particular insufficient prescription. It does not take treatment follow-up into account, especially monitoring of ADRs (only duration of treatment is taken into account after the initial prescription).

ACOVE

The most wide-ranging project, the Assessing Care of the Vulnerable Elder (ACOVE) project, is based on a systematic review of publications analysed by a group of experts in order to develop a set of indicators of quality of care that are relevant to frail elderly subjects. About one-third of indicators refer to medications.[43] The ACOVE indicators have several advantages:

- They include specifically geriatric situations (dementia, falls).
- They refer to treatment, prevention, education and diagnostic documentation.
- They include the three types of non-optimal prescriptions, in addition to monitoring.
- The majority of the indicators are applicable to patients with advanced dementia or an unfavourable prognosis.

However, the ACOVE publications are of uneven quality and their recommendations are sometimes in contradiction with analysis of the literature. These publications may also be considered as a collection of recommendations rather than indicators of clinical practice as such.

Key points

- Two possible meanings of 'drug misuse' are 'drug abuse' such as consumption of illicit substances or incorrect use of prescription drugs and suboptimal prescribing such as licit medication prescribed in an inappropriate way or considered insufficiently prescribed.
- Optimizing treatment consists in adapting the patient's treatment to their disorders: chronic conditions, acute conditions requiring overall reassessment of treatment, signs and symptoms and overall gerontological evaluation, taking into account the present state of scientific knowledge.
- Adverse drug reactions in the elderly appear to be due above all to defective monitoring rather than to an inopportune choice of medication. Consequently, it is more relevant to encourage good prescribing practices such as ensuring treatment follow-up and scheduling treatment over time than to stigmatize inappropriate treatments.

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CHAPTER 122

The use and abuse of prescribed medicines

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Introduction

Substance misuse occurs mainly in young adults, with most research focusing on this group. Several factors, however, suggest a growing trend towards substance misuse in the elderly, while a generation of lifetime drug users are now entering old age.[1] Along with the increase in ageing of European and North American populations, the number of older adults requiring treatment for substance misuse is predicted to double between 2001 and 2020.[2] The need for age-appropriate treatment interventions has never been greater.

Use and harmful use

When considering drug use among the elderly, it is helpful to consider substances of misuse in three broad categories: medications, both prescribed and non-prescribed; socially sanctioned psychoactive substances; and illicit substances. Self-evidently this classification will differ between countries due to religious, cultural and legal differences.[3] Among the elderly, drugs from the medicines category are overrepresented in people with harmful use when compared with other age groups.[4] This reflects the increased access to medicines among this group, allied to the physical and social barriers that make accessing other drugs harder for this group.

This chapter focuses on drug misusers who display 'harmful use', which is defined as 'a pattern of psychoactive drug use that causes damage to health, either mental or physical'.[5] The damage may be physical (as in cases of hepatitis from the self-administration of injected psychoactive substances) or mental (e.g. episodes of depressive disorder secondary to heavy consumption of alcohol).[6] It excludes cases where omission of a psychoactive medication may be harmful, for example, in cases of underuse of antidepressants.

Pharmacology

While drug absorption shows little variation with age, ageing results in an increase in the percentage of body fat, a reduction in lean body mass and a fall in total body water. Hydrophilic drugs, such as alcohol, are distributed in body water, such that with increasing age the volume of distribution falls and the peak concentration for a given dose may rise by 20%,[7] resulting in lower levels of intake giving the same intoxicant effect. Conversely, lipophilic drugs, such as benzodiazepines, that are stored in fatty tissue will remain in the body for longer, which could cause prolonged clinical symptoms such as disturbed cognition and mood.[8] A fall in plasma albumin in old age results in increased bioavailability of protein-bound drugs, such as warfarin and diazepam.

Drug elimination, through direct excretion or metabolism, is reduced in the elderly. Glomerular filtration rates fall steadily in old age, leading to the accumulation of renally excreted drugs. This may be compounded by renal damage due to drug misuse, for example, analgesic abuse.[9] Hepatic metabolism is reduced due to a reduced liver mass and blood flow, which may also be compounded by toxic drug effects. The efficiency of microsomal oxidation also falls with age, leading to reduced drug excretion of hepatically metabolized drugs.[10] The combination of these effects may greatly alter pharmacokinetics in the elderly. For example, the half-life of diazepam in the very elderly has been shown to be over 3 days, compared with 20 h in younger subjects.[11]

Multiple drug use complicates the pharmacokinetics of a substance, due to competition for binding sites and metabolic pathways. Polypharmacy has different effects, depending on whether it is acute or chronic. Alcohol will inhibit microsomal enzyme activity in acute use, while prolonged administration will induce the same enzymes. Hence alcohol will acutely raise concentrations of benzodiazepines, while lowering them if used chronically.[12]

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Pharmacodynamics also alter in the elderly. Few studies of age-related changes in the brain have focused on how these changes affect the function of the reward system and/or its sensitivity to drugs of abuse.[13] There are documented changes in the neurotransmitter systems (dopaminergic, glutamatergic and serotonergic) in the ageing brain. There is a reduction in dopamine receptor binding in the striatum, frontal cortex, anterior cingulated gyrus, temporal insula and thalamus plus the same change in *N*-methyl-D-aspartate (NMDA)-type glutamate receptors in the cortex, striatum and hippocampus.[13]

Prevalence and correlates

The elderly may display harmful use of any psychoactive substance. Illicit drug use is not commonly observed in the elderly, but numbers are on the rise.[14] Shah and Fountain identified the following as factors associated with illicit drug use in the elderly: male gender, 'young old' age group, belonging to the post-War cohort, African-American ethnicity, prior convictions, diagnosis of mental illness or alcohol misuse, serious medical illness and past history of substance misuse with onset before age of 30 years.[15]

Benzodiazepines

Benzodiazepines are the most frequently abused prescribed medication in elderly people.[16] Chronic use may contribute to toxic effects, including cognitive impairment, poor attention and anterograde amnesia, cerebellar signs such as ataxia,[17] dysarthria, tremor, impaired coordination and drowsiness,[18] depression and cognitive decline.[13] Increased falls and hip fractures are associated with benzodiazepine use in the elderly.[16,19–21] The risk is especially high within the first few weeks of use.

Withdrawal may be accompanied by rebound insomnia, agitation, convulsions and an acute confusional state. If benzodiazepines are required for the elderly, then short-acting drugs (i.e. with half-life less than 24 h) at the lowest effective dose may be used for a short duration.[22] There is no 'safe' period of use but tolerance and dependence levels increase with prolonged use.[23]

Prevalence of benzodiazepine use

Establishing levels of benzodiazepine amongst the elderly is problematic. National prescription audits can reflect trends in use but are unhelpful when considering particular population subgroups.

Following the publication of guidance for the appropriate use of benzodiazepines by the Committee on Safety of Medicines (CSM) UK in 1988,[24] prescribing of benzodiazepines has fallen dramatically. In England and Wales, prescriptions fell by 32% from 1987 to 1996.[25] Of concern, however, is that 30% of prescriptions were for long-term treatment and 56% of prescriptions for the three most commonly prescribed benzodiazepines were issued to patients over the age of 65 years.[26]

A community follow-up study of 5000 over-65s in Liverpool[17] revealed that 10% were using benzodiazepines on first assessment and that of these about 70% were taking a benzodiazepine 2 years and 69% 4 years later. Women were twice as likely to be taking a benzodiazepine as men at any stage in the study. In the USA, a study found 6.3% of a large sample of over-65s used a hypnotic, one-third of these daily and nine-tenths for at least 1 year.[27]

Use of benzodiazepines in institutional cohorts has traditionally been higher and associated with female gender, greater age, bereavement and poor health.[28] Chronic benzodiazepine use in older adults in nursing homes has been associated with depression, sleep disturbances and demand for medication.[21] In the USA, a study found that one-quarter of nursing-home residents were prescribed a benzodiazepine and nearly 10% of all residents had chronic benzodiazepine use.[29] Studies from other countries revealed similarly high levels of benzodiazepine use among institutionalized older adults.[29]

Psychiatric morbidity

Significantly high rates of psychiatric disorder have been described among elderly benzodiazepine users.[30] Benzodiazepine misuse happens in comorbidity with anxiety disorders[31,32] and affective and sleep disorders.[32] The incidence of comorbid alcohol abuse has not been consistently shown to be significantly greater among benzodiazepine misusers.[31] However, more recent research suggests that a prior history of alcoholism may predispose to later benzodiazepine misuse in the elderly.[16] Benzodiazepines are also used to reduce the undesirable effect of those substances.[32]

An all-age study found that DSM-III-R Axis I comorbidity existed in all cases of a sample of benzodiazepine-dependent users in Spain.[32] The commonest diagnoses were insomnia, anxiety disorders and affective disorders. Obsessive–compulsive, histrionic and dependent personality disorders were found in half of cases and physical problems in one-third of cases.

Depression can occur during the use and anxiety during the withdrawal. During use and withdrawal, some patients can suffer from psychotic episodes with hallucinations and delusions; nocturnal restlessness, paradoxical excitement and delirium.[33] The risk of suicide also increases.[8]

Gender and age

Benzodiazepine use is over-represented among women of all ages. The likelihood of use of a benzodiazepine increases with age. There is little evidence that this gender divide

narrows on reaching old age. Legislative approaches and prescribing guidelines have made some inroads into the over-representation of prescribing to the elderly.[34] Increasing public awareness of the side effects of benzodiazepines and an increase in advocacy services for the elderly are likely to have a similar effect.

Illicit drug misuse

Unfortunately, the prevalence of substance misuse in the elderly has not been investigated thoroughly, partly because substance misuse had not been considered to be a common health problem in this population. Overall, the prevalence of illicit drug use in the elderly is low compared with younger people.[15]

In the Epidemiological Catchment Area (ECA) Study, only 0.1% of elderly subjects met the criteria for drug abuse of an illicit substance in the previous month. Lifetime prevalence was 1.6% for over-65s.[35] Figures from the 2005 and 2006 National Survey on Drug Use and Health found similar low rates in the elderly along with higher rates in the middle aged, lending further evidence to the suggestion that prevalence rates may rise in the elderly as the younger cohort ages.[36] It has been estimated that as the baby boom generation reach older age, the number of elderly drug users will also increase in the Western world. Gfroerer and co-workers predicted that, compared with 2000, by 2020 there will be a 50% increase in number of older adults and a 70% increase in treatment need among them.[14] These predictions were replicated in other studies.[37]

In the UK, few cases of illicit drug use among the over-65s have been reported in the literature; one exception is a series of seven elderly subjects reported to have initiated injecting heroin in later life. They attributed their behaviour to a combination of loneliness and depression.[38]

In the USA, in a study of a Veterans' Administration old age psychiatry inpatient facility, 3% of the patients were found to have a primary drug misuse disorder involving prescribed medication, while 1% were addicted to illicit substances.[16] Also in the USA, attendance at methadone maintenance clinics by the elderly is reported to be rising, although over-60s still form only 2% of those attending.[4] Similarly, a number of elders are reported to continue their use of cannabis into late life.[39]

Explanations for the lower prevalence of drug misuse among the elderly include increase mortality among younger substance misusers, maturation out of substance misuse habit, poor identification of elderly cases and low acceptability of substance misuse among elderly people.[15]

Aetiology

There is a significant difference between the elderly drug user and the younger generation which leads to further marginalization of this group. The concept of marginality is introduced in this context to describe this group who live at the periphery of two cultures and do not belong to either, that is, they are marginal among a marginal group.[40] The result is a feeling of loneliness and the potential of being targeted in these 'old school' substance misusers. As they grow older, the nostalgia and idealization of the past feed back to this sense of loneliness. The role of drugs as a means of coping with loss (of loved ones, of children leaving home, retirement) has also been proposed.[13]

There are several theories on the aetiological role of the psychosocial factors.[41] They include:

1 *Social Control Theory:* Weakness of the strong social bonds that promote engagement in responsible behaviour precipitates engagement in undesirable behaviour, such as substance misuse. According to Moos,[41] the elements in operation in this model include weak attachment to existing social standards along with inadequate monitoring and goal direction.

2 *Social Learning Theory:* The attitude and behaviour of people who serve as the individual's role models play a crucial part in this model. Observing substance misuse by one's role models promotes the same behaviour in the individual through psychological processes of modelling and reinforcement.

3 *Behavioural Economics or Behavioural Choice Theory:* This approach identifies the importance of the social context. Lack of alternative rewards for activities other than substance misuse contributes towards its initiation and maintenance. Those activities include educational, social and also physical activities.

4 *Stress and Coping Theory:* Stressful life operates through increasing distress and alienation to increase the risk of substance misuse. Different stressors have been identified, such as childhood abuse and conflicts. Stress affects a person's self-confidence. Substance misuse is employed as a way of avoidance of coping.

Polysubstance misuse

The elderly have access to a variety of drugs of misuse. In many cases they may misuse one drug without misusing others. This is often the case with prescribed medication, where one medication is overused whereas compliance with the prescription is maintained for the others. Where non-prescribed substances become involved, the possibility of abuse of more than one substance is elevated. Finlayson and Davis [30] found that 15% of over-65s requiring inpatient detoxification from alcohol were also dependent upon a second substance, usually a hypnotic, anxiolytic or analgesic. The phenomenon of cross-tolerance must also be considered. Psychoactive substances may have a cumulative effect, due to either a shared outcome effect or to different drugs acting as interchangeable substitutes for

one another (cross-tolerance). Cross-tolerance exists within each class of drug, such that the clinician should always consider the total benzodiazepine or opioid dose, using class-specific equivalence charts.[42] Cross-tolerance for some drugs may also occur outside the class, most notably for alcohol and benzodiazepines. While this phenomenon is widely exploited for detoxification, failure to consider the clinical possibility may lead to cases of dependence being overlooked.

Detection

Self-presentation by elders may be limited by a number of factors.[43,44] Elders may not realize that they are ill or may not realize that the medical profession identifies substance misuse as an illness and will offer help. Also, the elderly are more likely to under-report their substance misuse.[45] Traditional forms of service promotion may fail to reach the elderly, and a service staffed by young professionals may seem intimidating or inappropriate for someone much older, particularly if their substance misuse is associated with a high degree of shame. Greenwood[46] argued that substance misusers, and the elderly in particular, suffer as a result of stigmatization, as their disorder is perceived as self-inflicted. This stigma may be reflected in a clinician's reluctance to become involved by acknowledging the problem. Unfortunately there is evidence that physicians find it hard to discuss substance misuse with the elderly.[13]

If self-presentation is unlikely, then the number of professional caregiver contacts that the elderly have provides a further opportunity for education about the problem and potential sources of help. This resource appears underdeveloped at present, with a need for better training for carers in identification of at-risk individuals and in appropriate actions once misusers have been identified.[47]

Detection of benzodiazepine use

Appropriate prescribing of sedatives for time-limited periods should be accompanied by vigilance for drug-seeking behaviour. Such behaviour includes early requests for repeat prescriptions or requests for increased doses. The elderly may also receive medication from multiple sources. Careful exchange of clinical information is vital in such settings. With these considerations in mind, the need for dependence-inducing drug prescriptions should be regularly reviewed and comorbid contributory conditions, such as depression, should be actively treated. Changes in legislation on prescribing practice may reduce the opportunity for drug misuse.[34]

The Severity of Dependence Scale has been validated as a screening tool for benzodiazepine dependence:[48]

1 Did you think your use of tranquillizers was out of control?
2 Did the prospect of missing a dose make you anxious or worried?
3 Did you worry about your use of tranquillizers?
4 Did you wish you could stop?
5 How difficult would you find it to stop or go without your tranquillizers?

Each of the items is scored on a four-point scale (items 1–4, 0 = never/almost never, 1 = sometimes, 2 = often, 3 = always/nearly always; item 5, 0 = not difficult, 1 = quite difficult, 2 = very difficult, 3 = impossible). A total score of 6 or more indicates problematic use, with a specificity of 94.2% and a sensitivity of 97.9%.[48]

Treatment

Treatment of substance misuse is a multistage process involving the integrated use of physical, psychological and social interventions. These interventions should, where possible, run concurrently as opposed to consecutively and must be provided in a form that is acceptable to the individual and sensitive to the specific needs of the elderly.[45] Amongst this client group, individuals rarely present complaining directly of a substance misuse disorder, but may present with associated physical problems. The first step of treatment is the identification of cases. This requires clinical observation allied to sensitive yet persistent enquiry. The routine use of standardized screening tools may help to focus clinical impression more accurately. Once identified as potential candidates for treatment, the patient's attitude towards their substance misuse requires examination. Exploration of the risks and a discussion of potential avenues for change may help to establish or reinforce the motivation to change. Drugs that cause significant physical dependence may necessitate detoxification regimens, while comorbid conditions such as depression that perpetuate the disorder need to be adequately treated. Social issues, such as housing and a social network that consists mainly of substance misusers, may perpetuate the problem and need to be examined for opportunities to change. The individual requires psychological rehabilitation to address the issues that may have contributed to the uncontrolled use of substances and to provide future coping.

Initiating treatment

There are no published data about the level of uptake of offers of help once elders abusing substances have been identified. However, elders do achieve equivalent or better results than younger adults when they do enter treatment.[2] Unfortunately, the pessimistic attitudes held by many professionals and carers towards the likelihood of successful resolution of the problem are frequently also held by the individual also. A fatalistic resignation to a life of substance misuse is often reported, particularly by long-term

users, whereas more recent onset users may express greater motivation for treatment.[49]

Once long-term use of benzodiazepines is established, dose reduction can be difficult to achieve. Withdrawal insomnia and rebound anxiety make patient motivation difficult to achieve. Where abstinence is desired, a conversion to a longer acting benzodiazepine and a gradual reduction in dosage over the course of months are advisable.[43] Rapid detoxification is associated with breakthrough withdrawal symptoms and may be complicated by convulsions. If a rapid withdrawal is necessary, it is best conducted in an inpatient setting if severe dependency is suspected. As with alcohol, the withdrawal period for the elderly is more likely to be complicated by confusion than in younger adults. Longer term prescribing of benzodiazepines should adhere to the following general principles: clear indication of benzodiazepine dependence, clear intermediate treatment goals, regular review and methods to prevent diversion.[50]

Psychological techniques, such as relaxation training and educative initiatives in the areas of sleep hygiene and correct medication use, may also prove valuable. Cormack *et al*.[51] demonstrated that writing to benzodiazepine users in primary care urging them to reduce their medication use resulted in a fall in total use by one-third over the next 6 months. Treatment of other forms of drug misuse in the elderly is under-researched. Misuse of analgesics may require formal detoxification if opioids are involved or physical dependence has developed. More often the patient requires information to allow them to make an informed choice about drug use and an alternative form of treatment for their condition. Still less information is available on the treatment of illicit drug use in the elderly, although several key publications argue for age-appropriate services to be developed.[2,45] These services should pay particular attention to comorbid health problems and should provide basic-level medical services.[2] Severe or complex health problems should be identified and referred to appropriate specialist services.

Psychological interventions

Once a patient is detoxified, rehabilitation is necessary to address the issues behind their substance use and to foster coping strategies for the future. Few studies have examined the particular needs of the elderly in a rehabilitation setting and have mostly focused on alcohol. Janik and Dunham reported on comparative outcomes for over 3000 over-60-year-olds and younger entrants into alcohol treatment programmes.[52] Outcomes after 6 months showed no differences between the groups.

Psychological programmes designed specifically with the elderly in mind may be more appropriate for consideration. Some success has been claimed for models encouraging the development of social networks with self-management skills.[53] Kofoed *et al*.,[54] in a small study, reported that retention in outpatient treatment of older adults was greater in an age-specific treatment group that focused on socialization and minimal confrontation (a mainstay of many programmes), compared with older patients in a mixed-age treatment group. At 1 year follow-up, the effect was lost.

Variations of the Alcoholics Anonymous 12-step model tailored to the needs of elders have been reported in the USA, with varying degrees of success.[55] Models low on confrontation, traditionally regarded as fundamental to overcoming denial on the part of the patient, appear to be supported by the work of Kashner *et al*.,[56] who found that 1 year follow-up of elders in a confrontational programme revealed half the levels of abstinence compared with a group in a programme where self-esteem, tolerance and peer relationships were promoted. Behavioural approaches, including cue identification and avoidance, have also been reported to be of clinical benefit.[53]

Even fewer age-specific studies are available to guide the clinician in the provision of aftercare to the elderly non-alcoholic drug user. An avoidance of drugs that have a dependence potential is advisable, if practical. Adequate rehabilitation and continuing support of the individual are indicated. This may be provided through generic old age psychiatry services or through specialist drug services, depending upon which service appears best able to cater for the specific needs of the user. The choice of service provider should reflect the lifestyle of the patient, as opposed to being a decision based solely on chronological as opposed to biological age. Further services may also be available in the form of mutual support groups similar to those available for alcohol.

Prognosis

In a survey by Moos *et al*., it was found that although the standardized mortality ratio (SMR) reduces with age among elderly people with substance misuse, it remains high, 1.66 in those >75 years of age.[57] They also found that patients with no outpatient mental health after discharge from inpatient intervention had a higher mortality, and in fact, intensive outpatient aftercare reduced the mortality rate in this group of patients. The effect could be through adherence to treatments (both psychiatric and medical), better housing and nutrition and better access to other forms of medical care.

Conclusion

Substance misuse and old age psychiatry have long been unpopular choices for specialization. Both fields are known for providing challenging patients with differing priorities to those of the clinician. Research in either field is

hampered by the difficulty in obtaining reliable clinical data on conditions for which few empirical measures exist. The field of old age substance misuse has suffered to some extent in clinical practice, where patients do not fit neatly into either service and are welcomed by neither. It is clear, however, that there exists a significant morbidity due to drug use in the elderly. The problem may be iatrogenic and autogenic in origin. Increased life expectancy and the cohort effect of generations of recreational drug users reaching old age are likely to intensify the problem. Adequate research to identify at-risk individuals and the provision of appropriate and accessible treatment services for the elderly drug misuser remain among the major challenges to healthcare providers.

Key points

- There is a growing trend towards substance misuse in the elderly, while a generation of lifetime drug users are now entering old age.
- When considering drug use among the elderly, it is helpful to consider substances of misuse in three broad categories: medications, both prescribed and non-prescribed; socially sanctioned psychoactive substances; and illicit substances.
- Treatment of substance misuse is a multistage process involving the integrated use of physical, psychological and social interventions.

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CHAPTER 123

Transportation, driving and older adults

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Introduction

The importance of transportation to health and social inclusion has been under-recognized in both the medical and the gerontological literature. Transportation is a crucial factor in maintaining older adult independence and the car is the most important source of transportation for older people.[1] Not only is community mobility a major priority for older people, but also problems with transportation have been recognized as barriers to access to healthcare for older people.[2] Concerns over access to adequate transportation among older people has been voiced by a number of international agencies, including the Organization for Economic Cooperation and Development (OECD)[3] and the Conference of the European Ministers for Transport.[4] This has been augmented by major national reviews which have also emphasized the need to adapt transportation systems to the needs of older people.[5]

However, the major emphasis of much of the medical literature on transportation and ageing is disproportionately skewed towards risk and crashes. This is particularly unfortunate, as older adults are the safest group of drivers[6] and even the often-quoted increased crash risk per mile is an artefact due to limited exposure or fewer miles driven per year. A number of studies have shown that the apparent increased crash risk disappears when one controls for mileage.[7] However, a major issue for older adults is an increase in crash fragility. Whether as car occupants[8] or as pedestrians, older people are more likely to suffer serious injury or death than middle-aged individuals given the same crash severity. In traffic terms, older adult fragility exposes weaknesses in the design of the traffic environment and vehicle. This clearly requires a societal response, in particular attention to in-car safety measures, which recognizes the altered physiology and increased frailty of older people. A good analogy can made with the danger posed by airbags for children who are front seat passengers: the response was not to stop children riding in cars, but rather to adapt the injury control measure (placing the children in the back seat, making occupants use seat belts).

For pedestrians, several responses are possible. Possibly the most important of these is to ensure that we do not unnecessarily turn older people into involuntary pedestrians through inappropriate driver screening programmes. There is evidence that this phenomenon underlies the negative impact of medically screening older drivers in Finland and Australia.[9–11] Other approaches include radically modifying traffic speed, allowing for the time needed for pedestrians to cross busy intersections, construction of safety barriers such as islands or walkbridges, better organization where vulnerable road users (pedestrians and cyclists) share the road with vehicular traffic and educating other road users to exercise caution in environments shared with older pedestrians.[12]

Illness and transportation

The most important impact of age-related illness on transportation is likely to be a reduction of personal mobility. This has been demonstrated for people with dementia,[13] but also happens with other illnesses. Older people report that impaired health is the most common reason for driving cessation.[14,15] However, patients rarely discuss this radical decision with a healthcare provider.[16] Physicians dealing with older adults need to be aware of these limitations and to be able to support their patients to maintain their independence.

The issue of crash risk has been overstated but sadly forms a negative public backdrop to our professional practice: a study of British and Irish media showed an overwhelmingly negative portrayal of older drivers, despite their excellent safety record.[17] Physicians must not allow a negative but inaccurate popular perception to interfere with their task of assessing, treating and advising older people in relation to their independence. This extends to the interpretation of studies on crashes: for example, certain illnesses are more common in older people who have crashes.[18]

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However, since older people have lower crash rates, the likelihood of effective public health interventions to reduce this low rate further are unrealistic and may cause further problems (e.g. driving retirement) recognized with screening of older drivers.

Clearly, for individual patients the maintenance of autonomy must be balanced with public safety to an extent consistent with that applied to the rest of the population. Age-related visual and cognitive diseases, in particular macular degeneration, Alzheimer's disease (AD), stroke and Parkinson's disease,[19] are likely to be the conditions most often associated with mobility and safety problems. Our main ethical prerogative is to preserve a sense of dealing with the issue in a hierarchical fashion common to good practice for all healthcare conditions. This emphasizes in turn the World Health Organization approach of health gain, health maintenance, compensation and finally palliation.[20]

The Older Drivers Project, an initiative between the American Medical Association and the US National Highway Traffic Safety Administration, has reaffirmed this principle, stating that a primary objective of its approach involves helping older drivers stay on the road safely to preserve their mobility and independence.[21] The Older Drivers Project recommends that this can be accomplished through three methods: (1) optimizing the driver, (2) optimizing the driving environment and (3) optimizing the vehicle. In this approach, driving cessation is recommended only after the safety of the driver cannot be secured through any other means.

Clinicians may be reluctant to address the driving issue in the office practice setting. There is a clear need for education in the assessment of mobility and driving: the good news is that such education appears to be effective.[22] Evaluating driving skills should not be viewed differently from the evaluation of risk for falls or other risk for injuries in older adults. Clinicians should consider the recommendation for driving retirement in older adults in a similar way to the decision that a previously ambulatory patient is now wheelchair bound for life: efforts should be made to preserve mobility when possible.

Definitive guidelines on how clinicians can intervene effectively to ensure adequate mobility, driving safety or effect driving cessation in impaired older adults are still needed, but current evidence and available resources indicate a general approach to this issue. There is an increasing body of evidence on the subject and some helpful guides.[23] In addition, the relatively broad approach to Comprehensive Geriatric Assessment means that geriatricians will better understand the limitations of a predominantly cognitive approach to driving assessment, even in conditions characterized by cognitive decline. A good proxy is entry to nursing home care, which is poorly predicted by individual's neurocognitive testing, but better matched by behavioural and functional limitations.[24]

Table 123.1 Schematic outline of driving assessment.

History
• Patient, family/informant
• Driving history
Examination
Functional status
Other illnesses and drugs
Vision
Mental status testing
Diagnostic formulation and prioritization
Disease severity and fluctuations
Remediation
Re-assess
± In-depth cognitive/perceptual testing
± On-road assessment
Overall evaluation of hazard
• Strategic
• Tactical
• Operational
Advice to patient/carer ± DMV/DVLA
If driving too hazardous, consider alternative mobility strategies

Of particular importance has been the recognition that a relatively wide number of interventions can improve driving ease and safety (Table 123.1). It is also remarkable that most reviews on medications and driving emphasize possible negative effects on driving, rather than reflecting that anti-inflammatory, anti-parkinsonian and antidepressant medications might actually improve driving ability and comfort! The possibility that cholinesterase inhibitors might improve or maintain driving skills in dementia is an interesting possibility.[25] Assistive technologies, such as global position system (GPS) devices, may assist some older adults with geographic orientation. Crash warning systems may also be of benefit. Preliminary data support cognitive stimulation[26] and exercise interventions[27] directed at driving-related cognitive abilities in older adults as being potentially beneficial. More intervention studies are sorely needed in these areas.

What do we need to know to assess our older patients?

Physicians assessing older people for transport/driving capability need to know:

1 How does the older adult meet their transportation needs?

2 What intrinsic factors contribute to driving ability and how can we assess them?

3 What common illnesses in later life can impair traffic skills?

4 What, if any, interventions should office-based clinicians pursue?

5 What is the physician's responsibility with regard to driver licensing and insurance authorities?

Taking a driving/transportation history

The interested clinician can check static visual acuity (Snellen chart), hearing (whisper test or hand-held audiometry), attention and reaction time (Trail Making Test A or B), visual spatial skills (clock drawing task), judgment, insight, joint range of motion and muscle strength.[40–43] Many of these tests were recently included in an American Medical Association resource on older drivers as reasonable for assessing and counselling older adult drivers and are available on their web site along with evidence-based medicine references. These tests are probably more important for gaining an overall perspective on the patient's abilities and disabilities, rather than relying overly on the performance of any one component.

Although it may seem obvious that transportation should figure in a comprehensive assessment, this is not necessarily the case. An extreme example of this is the failure of the referring physician to advise on driving restriction for a significant number of people referred to a syncope clinic.[28] It is also likely that many patients do not obtain formal advice or assessment about driving after stroke.[29] As there is potential to improve driving and transportation options, there is also a need to discuss restrictions or planned withdrawal from driving for many patients. There are data to suggest that license restriction is associated with lower crash risks.[30] Thus, a graduated driving reduction may be a viable option rather than driving cessation.

The patient's own assessment of driving should be assessed and a promising approach in this regard is the Adelaide Self-Efficacy Scale.[31] It is encouraging that self-assessed driving skills in mild cognitive impairment seem preserved.[32] A collateral (witness) history of driving abilities is important, given the often collaborative nature of driving in later life,[33] but cognizant of the conflict of interest of a spouse who does not drive.[34] Recent data indicate that informants are able to recognize impaired driving behaviour in some older adults with medical illness.[35]

What factors are important in driving assessment?

The greatest advance in this area has been the understanding that a purely cognitive model of driving ability does not adequately reflect the complexity and hierarchical nature of the driving task.[36] Psychometric approaches have generally been disappointing for a number of reasons[37] and efforts to find a best cognitive battery resemble the alchemist's search for transforming base metal into gold rather than a carefully thought out scientific endeavour. However, recent efforts have pushed correct classification rates in demented samples to 80%, which is encouraging.[38]

Currently, many prediction efforts have focused on heterogeneous groups of older adults during licence renewal. However, the crash rate of this group is already low (e.g. like the odds ratios for predicting crashes) and it is unlikely that any set of tests in this arena will be useful for the prospective prediction of driving safety. Further success at developing fitness-to-drive models will likely need to focus on specific groups of medically impaired older adults that are homogenous in their specific cognitive or visual domains (e.g. dementia with a specific subtype such as AD). In addition, these models will likely need to incorporate additional measures or proxies such as lifelong driving habits (e.g. history of tickets, crashes, abnormal driving behaviours), personality characteristics (e.g. too aggressive or too passive), traffic density and perhaps other measurement concerns such as test anxiety or confidence issues.

The most common model for driver assessment would involve a combination of physician, occupational therapist, neuropsychologist, specialist driving assessor and/or social worker. Not all disciplines will be needed by all patients: a patient with severe dementia clearly cannot drive and simply a referral to the social worker to plan alternative transportation is appropriate. Equally, a mild cognitive defect may only require a review by the physician and occupational therapist. The overall interdisciplinary assessment should attempt to provide solutions to both maintaining activities and exploring transport needs. However, even in a skilled rehabilitation setting, the predictive value of team assessments may be low for diseases such as stroke[39] and the on-road test is the current best assessment available.

The on-road test may be helpful, as it may demonstrate impairments to a patient or caregiver who is ambiguous about the patient stopping driving. At a therapeutic level, members of the team may be able to assist the patients in coming to terms with the losses associated with stopping driving. The occupational therapist may be able to maximize activities and function and help focus on preserved areas of achievement, while the social worker can advise on alternative methods of transport. This approach should save time and valuable resources for occupational therapy, neuropsychology and on-road driver assessors.

In addition to the usual work-up, the medical assessment should include a driving history from patient and ideally (with the patient's permission) also from a caregiver or informant. The physician needs to weigh judiciously the collateral history, taking into account whether or not the carer is also dependent on the patient operating a motor vehicle. Physicians should also inquire about new unsafe driving behaviours. These behaviours can be apparent in mild dementia and would raise concerns about continuing driving privileges. It is important to recognize that these behaviours represent a *change* from baseline. They include

becoming lost in familiar areas, driving too fast, reacting too slowly, consistently making poor judgments, failure to notice street signs, having more accidents, receiving indecent gestures from other drivers, miscalculating speed and distances, new dents on the car, knocking off rear-view mirrors, showing poor judgment when making turns or impaired ability to recognize or understand road or traffic signs.

The next stage of testing includes evaluations from occupational therapists and/or neuropsychologists. None of the studies have been sufficiently large to have a reasonable predictive value or to determine cut-off points on neuropsychological test batteries. This situation is paralleled in memory clinics where there is a wide variation in test batteries used: it is likely that the important elements of successful assessment are choice of key domains, familiarity with a test battery and the development of an understanding and close liaison between the physician and the occupational therapist and/or neuropsychologist. In addition, a recent review indicated that to date, there is little evidence to support the use of performance based road tests.

A wide range of tests have been correlated with driving behaviour but few have been sufficiently robust to calculate cut-off points for risky driving. All of these tests can be criticized for taking an over-cognitive view of the driving task.[44] A comprehensive review of tests is available from the US National Highway Transportation Safety Administration[45] and a recent meta-analysis limited to traditional neuropsychological tests indicated that visuospatial skill impairment was the cognitive ability with the strongest association with impaired driving in studies with dementia.[46]

The other interesting aspect is that there may be a disparity between scores on a test battery and the clinical assessment of the neuropsychologist. In a short paper by Fox *et al*., the neuropsychology test scores and the neuropsychology prediction were found not to be significantly associated, suggesting that the clinicians made their decisions on items not formally measured in the neuropsychology test battery.[47] In conjunction with the clinical assessment and collateral history, these tests will guide the physician as to which patients require on-road testing, and also those who are likely to be dangerous to test!

At present, simulators of sufficient sophistication are not widely available but may represent opportunities for both driver rehabilitation[48] (analogous to training aeroplane pilots) and assessment. The main benefit of large, sophisticated simulators such as the Iowa simulator has been to try to develop and understand neuropsychological and behavioural test batteries in a safe and reliable method and to correlate them with unsafe driving behaviour and crashes. The classic paper by Rizzo *et al*. in 1997 revealed that 29% of AD patients experienced crashes in the simulator versus none of 18 control participants.[49] The drivers with AD were also more than twice as likely to experience 'close calls'. There was also evidence that some drivers with mild AD did not crash and showed fair control of their vehicles compatible with the idea that some patients with mild dementia should be allowed to continue to drive.

On-road driver testing is the gold standard and should be offered to all patients who are not clearly dangerous when driving. The assessor will require a full clinical report and may choose to use one of the recently developed scoring systems for on-road testing of patients with dementia. At least three different road tests have been devised specifically for dementia, although the numbers put through these in published series are still relatively small, with 27 patients in the Sepulveda Road Test,[50] 65 in the Washington University Road Test[51] and 100 in the Alberta Road Test.[52] The tests should ideally involve some degree of cognitive loading, which will tend to bring out the degree and extent to which the older driver can manage complex situations safely.[53]

The quantification, operationalization and validation of these road tests need to be done repeatedly in environments other than that of the originators of the test. The current reliability of standardized tests seems promising.[54] An additional spin-off may well be that just as the simulators may provide information on which behavioural or neuropsychological tests might be helpful in deciding which drivers are safe to drive, so too may road test schedules help in the development of neuropsychological tests. Psychological batteries have been developed from both the Sepulveda and Alberta Road Tests.

There are certain limitations with road tests. Expenses for driving evaluations may vary from $200 to $500 and health insurance or government health providers may not cover the cost. In addition, they often occur in an unfamiliar environment and in an unfamiliar car. However, professional organizations representing geriatricians need to undertake advocacy to ensure that on-road testing is available, of a high standard and affordable to our patients.

What risks are associated with common diseases of later life?

Whereas early papers on dementia and driving emphasized the potential risks from those with dementia, subsequent research has not shown unequivocally that drivers with dementia pose a public health hazard. The precise contribution of the dementias to overall crash hazard is uncertain. Although Johansson *et al*. suggested a major role for dementia as a cause of crashes among older drivers on neuropathological grounds,[55] subsequent interview with families did not reveal significant problems with memory or activities of daily living.[56] The Stockholm group also showed that older drivers who had a high level of traffic violations had a high prevalence of cognitive deficits.[57]

Retrospective studies of dementia and driving from specialist dementia clinics tend to show a high risk,[58–60]

whereas those which are prospective and which look at the early stages of dementia show a less pronounced pattern of risk. In the first 2 years of dementia, the risk approximates that of the general population.[61,62] Controlled longitudinal studies of crashes and dementia showed no increase in crash rates for drivers with dementia.[63,64] Likely causes for this counterintuitive finding include a lower annual mileage, using state records for crash data and restriction of driving by the patient, family and physicians. Mild cognitive impairment (MCI), short of dementia, in some studies does not appear to have a significant impact on driving skills.[65,66] For MCI and impaired driving, see Frittelli *et al.* and Wadley *et al.*[100a,b]

Extrapolating from special populations may skew predictions of risk. For example, epilepsy, for which there are relatively clear-cut guidelines in most countries, would seem to pose a clear threat to driving ability as viewed from a clinic setting. Recent population-based studies seem to suggest that the increased risk is relatively low.[67] In a population renewing their licences in North Carolina, the lowest decile had a relative crash risk of 1.5 in the 3 years previous to the cognitive testing.[68] A somewhat reassuring finding from this cohort is that those with the poorest scores for visual and cognitive function also drove less and avoided high-risk situations.[69] A reasonable conclusion from these studies is that dementia among drivers is not yet a public health problem. Although increasing numbers of older drivers may change this situation, it is also possible that 'Smeed's law' will operate, whereby increasing numbers of drivers among a defined population are associated with a drop in fatality rates per car.[70]

Older drivers report less driving at night or during adverse weather conditions and avoid rush hour or congested thoroughfares. Most importantly, cognitively impaired older adults who renewed their licence appear to restrict their exposure even further, many to less than 3000 miles per year.[69] Demented drivers may further limit their exposure when compared with age-matched controls.[71] The data on exposure will require some confirmation, since there certainly are questions raised regarding the accuracy of reporting mileage in any cognitively impaired group. However, decreased exposure may explain why many crash studies have not observed major differences in crash rates from controls when comparing rates on the number of crashes per year and not factoring in total mileage.[72]

Polypharmacy is common in older adults and medication may be additive to crash risk in older adults with cognitive impairment. This is a complex area and it can be difficult to tell whether it is the illness or the medication which is causing the problem. There are many medication classes that have been studied and noted to impair driving skills when assessed by simulators or road tests, although these decrements may not translate into increased safety risk. These include, but are not limited to; narcotics, benzodiazepines, antihistamines, antidepressants, antipsychotics, hypnotics, alcohol and muscle relaxants. Very few studies have focused on the older adult driver. However, long-acting benzodiazepines have been associated with increased crash rates.[73] Another report suggests that there may be a significant number of older adults driving while intoxicated or under the influence of other medications.[74,75] Clinicians should review medications closely with each individual and attempt to discontinue medications that have the potential to affect cognition adversely when appropriate. Screening for alcohol abuse or misuse is also reasonable.

What interventions can we make?

Depending on the illnesses present, there is potentially a wide range of interventions that we can undertake (Table 123.2). Adaptation of the car, following advice from the occupational therapist, physiotherapist or specialist driving assessor, can improve driving comfort and safety. A follow-up review should be organized for those with progressive illness such as dementia and parkinsonism.[76] A review period of 6–12 months would seem to be reasonable with a progressive neurodegenerative dementia.[77] However, patients and carers should be asked to seek an earlier review if they perceive a significant decline in the status of the dementia or in driving abilities. Although some studies have concluded with recommendations that all older adults with dementia should refrain from driving,[58] the majority of clinicians would likely base this decision on dementia severity[78] or a demonstration of impaired driving competence.[79] The American Academy of Neurology guidelines, proposing that no-one with a Clinical Dementia Rating (CDR) Scale of 1 should drive, have been superseded by research that judged 41% of those with a CDR 1 as safe (19% were considered to be marginal and 41% to be unsafe).[77] This reinforces the need for a full assessment and appropriate follow-up.

For progressive neurological conditions, the physician needs to help the patient and their family prepare for eventual withdrawal from driving. Early and appropriate diagnosis disclosure is likely to be important here.[80] A helpful description of this process is the modified Ulysses contract,[81] after the hero who made his crew tie him to the mast on the condition that they did not heed his entreaties to be released when seduced by the song of the sirens. It forms the basis of a useful patient and carer brochure from the Hartford Foundation, which is also available online.[82]

The very act of highlighting the potential of compromised driving ability may have a therapeutic benefit, promoting increased vigilance on the part of the patient and carers that their social contract for driving privileges is not the same as that of the general public. Support is given to this concept by the success of restricted licensing for people

Table 123.2 Sample diseases for which appropriate assessment and remediation may be of benefit.

Neuropsychiatric	
Stroke	Driving-specific rehabilitation[89]
Parkinson's disease	Maximizing motor function, treatment of depression, assessment of cognitive function[90]
Delirium	Treatment and resolution
Depression	Treatment: if antidepressant, choose one with least potential of cognitive/motor effects [91]
Mild dementia	Assess, treat depression, reduce/eliminate psychoactive drugs, advice not to drive alone[92]
Cardiovascular	
Syncope	Advice pending investigation: treat cause[93]
Respiratory	
Sleep apnoea	Treatment of underlying disease[94]
Vision	
Cataract	Surgery, appropriate corrective lens and advice about glare[95]
Metabolic	
Diabetes	Direct therapy to avoid hypoglycaemia[96]
Musculoskeletal	
All arthritides	Driving-specific rehabilitation programme[97]
Iatrogenic	
Polypharmacy	Rationalize medications[98]
Psychoactive medication	Rationalize, minimize[99]

with medical illnesses in the State of Utah.[83] While the effect might arise from the restrictions (avoidance of motorways, night-time driving), it is also possible that the very act of labelling these drivers may heighten self-awareness.

A clear recommendation should be made to the patient and recorded in the medical record; this should include advice to inform their insurance company of relevant illnesses, and also any statutory requirement to inform their driver licensing authority.

When driving is no longer possible, alternative options should be discussed with the patient. For the fortunate minority who have access to a paratransit system (tailored, affordable personal transportation systems[84]), the graduation may be more easy. For the rest, although public transportation systems[85] may have reduced fares for senior citizens, the very disabilities that prevented driving also render such services sub-optimal.[86] Due to restricted sites and cognitive limitations of our older drivers, these services are typically underutilized, and simply not practical. State or locally sponsored services may provide door-to-door transport for older adults in large vans, many of which are lift-equipped. Local communities, societies, retirement centres or local church groups may use funds or volunteers to provide services to physician offices, shops and meetings. Transportation is often provided by family members once the older adult can no longer perform the task.[87,88] More unique and novel transportation services are needed and those such as Independent Transportation Network America (www.itnamerica.org) give promise to future older adults that have lost their privilege to drive.

What is the physician's responsibility with regard to driver licensing and insurance authorities?

In general, the welfarist role of the physician extends to reminding the patient that most insurance companies require disclosure by the driver of 'illnesses relevant to driving' when they arise. Two issues arise: the medical advisers of the insurance companies may not make calculations of insurance rates (or continued insurance) on the basis of reason and evidence but rather on ageist grounds and prejudice against disability. We may be unwittingly exposing the patient to this prejudice. The answer to this lies in continued advocacy efforts of professional groups at a societal level and also support by the physician in individual cases if the assessment supports preserved driving skills. A second issue is whether it is sufficient to recommend disclosure to someone who will not remember this advice. However, the physician's role is primarily to ensure safe mobility. In general, it is reasonable to assume that removal of insurance coverage is a secondary matter in such cases. It is reasonable to share the disclosure information with the carers.

The actual process of breaking confidentiality in the event of evidence of hazard to other members of the public is almost universally supported by most codes of medical practice – but it is to whom this should be reported that poses some ethical challenges. The traditional route of reporting to driver licensing authorities [DMV (USA), DVLA (UK)] may have relatively little benefit – removal of a driving licence is a dramatic event and may possibly be remembered by even a driver with moderate dementia. It is important that this disclosure has some likelihood of impact and results in the least traumatic removal of the compromised older driver from the road. In such instances, the family may be able to intervene in terms of disabling the car and providing alternative modes of transport. In our own experience, we rarely have to invoke official intervention, but find that a personal communication with a senior police officer in the patient's locality may result in a sensitive visit to the patient and cessation of driving.

Mandatory reporting represents a different ethical challenge. It has not been shown to be of benefit and, unless

significant benefit can be shown in future studies, the profession should resist the introduction of such schemes. For individual practitioners in jurisdictions where such regulations exist, a twin-track approach is probably necessary – professional advocacy with law-makers and a considered approach as to whether disclosure is in the patient's best interests on a case-by-case basis. If the physician is confident that the state or province has a mechanism for fair assessment and an enlightened approach to maintaining mobility, compliance is not difficult. If the assessment is cursory and aimed at unduly restricting mobility, physicians may be faced with a problem recognized with other laws, which may put patient's welfare at risk and where professional obligations may require non-compliance with an unfair law.

Conclusion

Transportation and driving assessment have become an integral part of the assessment of older people. Geriatricians, appropriately supported by their interdisciplinary team and specialist on-road assessment, can help to support safe mobility and social inclusion in later life. There is a need for more research to clarify further the most appropriate and economical assessments and interventions which further this end.[3]

Key points

- Transportation is an important component of well-being for older people.
- In contrast to previous attitudes which prioritized risk over mobility, current thinking and practice promote the optimization of mobility for older people.
- Geriatricians, appropriately supported by their interdisciplinary team and specialist on-road assessment, can help to support safe mobility and social inclusion in later life.

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CHAPTER 124

Smart homes

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Introduction

Smart homes have been in existence for many years, primarily pursued by those with a love of high-tech living environments. However, despite their rather pretentious label, this technology can provide many benefits to support elderly people and there is a growing body of experience which demonstrates its potential. This chapter looks at the ways in which smart homes can provide support based on the experiences of a number of groups. It considers the issues that have to be addressed if it is to be successful, together with some of the growing evidence for its effectiveness and it concludes with a look at the future of this work.

What is a smart home?

The term 'smart home' has been confused by some by using it to describe technology that relies on sensors in the home that can send messages to call centres. Such technology is really telecare and will be referred to as such in this chapter. The primary property that endows a house with the smart home label is its ability to support the user in an autonomous fashion. In other words, it can monitor the user's activities and the way they interact with appliances in the home, but it is also able to supply a response itself to support the user. For example, if a smart home detects a running bath being nearly full it will respond by turning off the taps rather than calling for someone to come and intervene.

What needs to be incorporated in a house to enable it to qualify for this lofty label? A smart home requires three facilities to be installed in order to operate (see Figure 124.1). First, it requires sensors that can monitor the occupant's behaviour and activities as described above, for example, by sensing the water level in a bath. Second, it requires a series of support devices so that it can autonomously provide the backup needed to support the user, for example, means for automatically turning off the bath water. Third, the particular feature that distinguishes a smart home, it requires a means whereby all the sensors and the support devices can talk to each other. This facility is achieved through the use of a communication bus, which is conventionally a form of wiring that enables messages to be sent between the sensors and the support devices, although increasingly it is embodied in a wireless form. The communication bus is linked to a computer or other logic controller that can see all the information being provided by the sensors and which can then make judgements about the user's behaviour. If it decides some action is needed, then it can initiate the activities of the relevant support device.

Hence there is nothing particularly complicated about smart technology. It has been around for a long time in installations in larger public buildings such as airports and hotels. In such buildings, the technology primarily enables environmental control to be provided autonomously so that the building is able to ensure that appropriate temperatures, ventilation and so on are maintained automatically. The communication bus, a key feature of such installations, has been the subject of some standardization so that different manufacturers' components can talk to each other. Many of the components developed for these purposes, such as lighting controls, can be directly applied to usage in domestic homes (Figure 124.2).

Applicability to elderly people

Given the ready availability of smart home components, a number of groups have explored the possibility of using them in a domestic setting to provide support that augments the help received from carers. A lot of work has been carried out to see if people with physical disabilities can be supported. The Edinvar Housing Association in Edinburgh undertook pioneering work to explore the potential of this technology. The Joseph Rowntree Foundation (JRF) has provided a number of installations in York with a fair amount of success. The JRF has published a number of guides about the technology.[1,2] Some

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

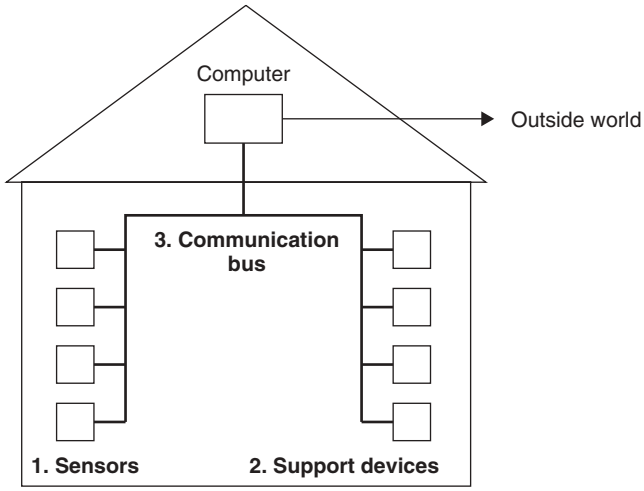

Figure 124.1 Components of a smart house system.

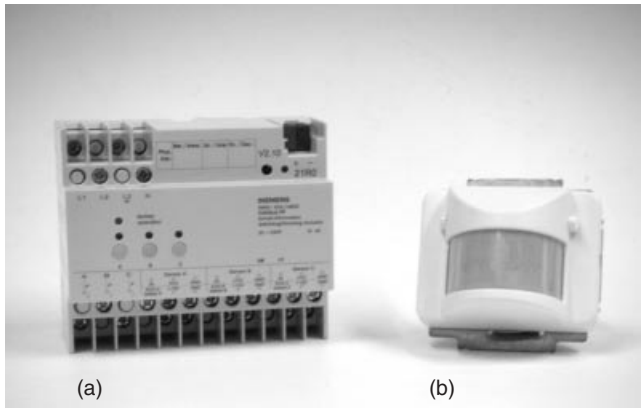

Figure 124.2 Standard commercially available smart home components: (a) a light fader unit and (b) a passive infrared sensor.

pioneering work in Norway has also explored the potential of this technology to support people with dementia.[3] The installations have primarily used commercial smart home components developed for public buildings and configured them in a form that allows their use in a domestic environment. More recently, purpose-designed technology has been developed, such as work at Brunel University on the Millennium Homes project,[4] which enabled the home to give voice prompts to the user to check if they needed outside support.

The majority of these installations have used the ready availability of smart home components to provide the technology that is used. For lighting and ventilation, these components are very appropriate. However, there are a number of situations where such technology is not so appropriate and where support devices need to be better tailored to the needs of the end user. A typical example is the use of commercially available technology to provide tap control. Several installations have used taps controlled by an infrared sensor that could be very useful for someone with poor hand function. All the user has to do is wave their hands in front of the sensor, usually mounted just underneath the tap, and water will be provided while the hands are in position. However, this operation is somewhat unnatural and for someone with a cognitive problem such taps would be totally confusing. These kinds of installations take a somewhat technology-led approach to their design. In other words, the installations start from looking at what technology is available and then configuring it in a form that seems to be close to providing the support needed.

The work carried out at the Bath Institute of Medical Engineering on the Gloucester smart house project explores these issues from a somewhat different perspective.[5] This project is aimed specifically at supporting people with dementia and uses a design technique that is very user-led. In other words, user needs are explored initially to provide a definition of the kind of problems that have to be supported by the technology. Having made these definitions, the design work then moves on to create purpose-designed devices that provide the care needed.

Ensuring user friendliness

There is, of course, a spectrum of reaction to technology on the part of elderly people in the same way as there is for any other age group, and some elderly people are very excited and very proficient in using equipment such as computers. However, there is no doubt that interaction with sophisticated technology can cause a lot of anxiety, which may deter many people from using it. Consequently, when it comes to providing supportive technology for the majority of users, it is preferable that the cognitive load on the user is kept as low as possible. The technology should really provide support with as little intervention as possible from the user.

The problems of designing user-friendly installations are exacerbated when it comes to providing support for people with dementia. For such a user group, having to learn new skills or make sense of a new piece of technology is out of the question. The technology really does have to be invisible and just intervene and provide support when the house deems it to be necessary. The technology has to be totally in the background, where the home appears to be just the same as any other home, where the user does not have to learn any new skills or interact with the new technology. But such installations are also going to be very user friendly for more cognitively able users and will be suitable for those who are less able to cope with new technology. Design approaches that embody this approach have been published.[6,7]

The individual nature of the problems faced by older people has a big impact on the installation of smart home systems. As with all assistive technology, any means of tailoring it to the needs of the individual will make it more effective. Smart home technology is inherently flexible in that the way in which a system responds depends on the control software and this in turn can be easily configured for the individual. Ideally, installations need to be set up for an individual client by a non-technical professional such as an occupational therapist (OT), and this in turn means that such configuring interfaces also need to be user friendly.

Some examples of usage

A few examples can illustrate how new technology can be supportive of someone but require little or no learning. A situation that causes a lot of concern is the problem of an elderly person getting out of bed at night and finding the toilet. For someone who may be unsteady on their feet, rising from lying down to standing is particularly dangerous. The problem is exacerbated by the fact that they are probably in a dark environment. How can smart home technology assist in this situation? First, the house can know whether it is dark or not through ambient light sensors. It can also detect whether someone is in bed and about to get up by means of bed-occupancy sensors. These can be placed underneath the bed legs or across the mattress to detect a weight change (see Figure 124.3). Sometimes pressure-sensitive mats are used on the floor next to the bed, although experience has shown that some users will make a point of not treading on the mat once they have learnt that it is there. Given this information, the house can ensure that when someone gets out of bed in the dark the bedroom light or a bedside lamp is turned on. To reduce the possibility of alarming the user, the light can be activated through faders so that they fade up to a fairly low level in a gentle manner (Figure 124.4). In this way, the user is provided with lighting to help them orientate more easily and move around without tripping or bumping into things. The process can also be reversed. If the user gets back into bed but forgets to turn off the light, the house can again detect that this has happened and can turn the lights off automatically.

Figure 124.3 A bed-occupancy sensor that fits under a bed leg.

Figure 124.4 An automatic bedside lamp in use.

This simple use of smart home technology can be taken further. The movements of an occupant about a room can be easily and reliably detected using passive infrared sensors (PIRs). These are the kind of sensors that are used in most home security systems and burglar alarms. It is easy to arrange for lights to come on automatically as the user moves around the house, again ensuring that they have illumination and help reduce falls. If the user has got out of bed and begins to go out of the bedroom, the house could make an initial assumption that they probably want to go to the toilet. It could then fade up the toilet lights and fade down the bedroom lights. In this way, it provides guidance to the toilet for the user. When the user has finished in the toilet and begins to go out of the bathroom, the house could reverse its response, fading up the bedroom light again and fading down the toilet one. In this way, the house can provide guidance to the user moving around the house in addition to providing illumination.

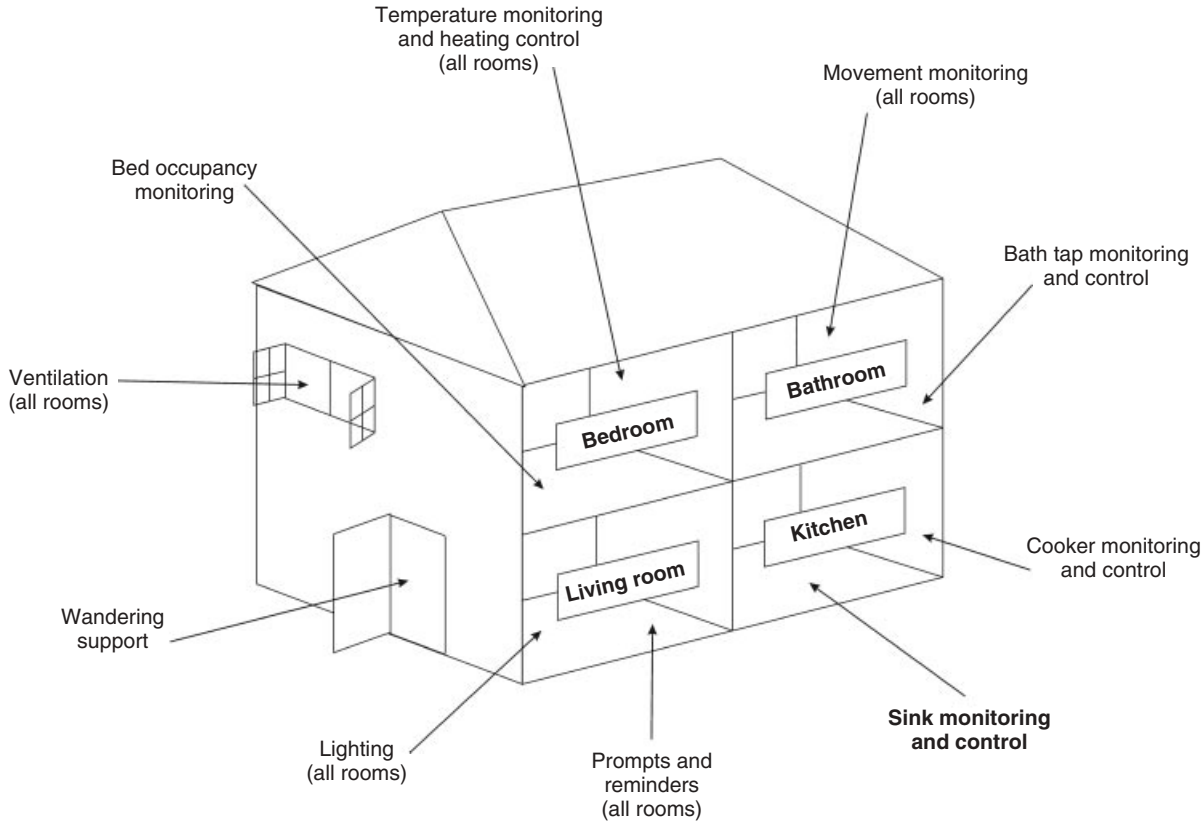

Figure 124.5 Possible support that can be provided by a smart home installation.

There are many other ways that smart house technology can provide support to the occupant (see Figure 124.5). For example, the house can detect if something slightly dangerous has been done, say in the kitchen, and then provide prompts and support. In a similar way, the use of other domestic appliances such as the bath and the kitchen sink can be backed up by keeping water temperatures safe and turning off taps as described above. For people with dementia, the house can keep an eye on wandering tendencies and try to discourage going out of the house and calling for help if it occurs. The house can also provide prompts for activities that need to be carried out such as taking medication or provide a form of day diary to remind people of visitors or mealtimes or even a favourite TV programme. In many ways, the house acts like an extra carer, but one that acts for 24 h per day without becoming tired or frustrated. However, of course it can never supply the qualities of personal human care and it is crucial that installers bear this in mind and do not just see smart homes as a cheap replacement for normal caring.

Appropriate design

Simple application of smart home technology can, in the ways illustrated, provide a lot of support for the user. However, if it is to be effective it has to be designed from a close understanding of the issues that are likely to arise and the way in which users are likely to interact with the technology. A very useful rule of thumb that was used in the development of technology within the Gloucester smart house project was to try to design new support equipment that reacted in a way that emulated the behaviour of personal carers. The reasoning behind this approach was that in many circumstances a personal carer is likely to be the person who best understands what works in caring for the person they are looking after. If they have developed a strategy that works for them, it is likely that any new technology that reacts in a similar way is going to be helpful. Surveys of personal carers showed that there was often a good consensus about strategies found to work. This understanding was a starting point for the new technology developed by the team for use in a smart home. During the design and development work, whenever a situation arose where it was not clear how the technology should react, it was found to be very useful to ask, 'What would the carer do in this situation?'. In this way, the technology is being designed to act as a kind of invisible carer that is ever present, just looking over the user's shoulder, checking that things are alright and just providing help when needed.

A good example of the use of the 'carer emulation' approach is provided by the designs used to control a bath. It would be easy to install a bath water-level sensor that shuts off the water supply when the bath is nearly full. Such a facility would ensure that a forgetful user did not flood the bathroom. However, if they came back to add some more hot water or they let out the water and wanted to run a bath the next day, they would find that the taps did not work because the water had been shut off. A key element in maintaining quality of life for someone with a cognitive problem is to enable them to feel they are still in control of their lives, and finding that their house is taking that control away from them would be counterproductive. How would a carer react to the problem of someone forgetting they were running a bath? It was found that, in these kinds of situations, the carer would follow a simple three-stage response. They would first provide a reminder, 'Don't forget you've got the bath running'. If that did not do the trick, they would then intervene to turn off the bath (or the cooker or other appliance). However, they would turn off the tap in the usual way, which would mean that it could still be used subsequently. Third, they would provide some reassurance to the user, such as, 'I've turned off your bath. It's ready now', so that the user knew why something had happened.

All these actions can be emulated by the smart home, but there is a need for some additional technology. There is a need for a means of communicating with the user, to provide prompts and reminders, and this was done through the use of voice recordings. There is also a need for a means of turning off the bath taps in such a way that the user can still carry on using it themselves (Figure 124.6). The redesigned taps had their insides removed and a new shaft was provided that was rotated when the tap was turned. The shaft was linked to a sensor that could monitor how far the tap had been turned. Hence all the new tap did was to sense how far the user had opened the tap. Depending on this information, an electric valve would open to let the water through at an equivalent rate. If the house needed to shut off the water, it could turn off the electric water valve and then apply an electric brake to the tap shaft. In this way, so far as the user was concerned, the tap felt like it had been turned off. The house would then reset the rotation sensor back to zero. If the user subsequently came to operate the tap, it would first of all feel like someone had turned it off, but it would also activate the sensor in the usual way and the electric valve would supply water. This novel tap design was not just an engineer's good idea about a new tap design, it was completely led by an understanding of the issues involved and the way in which the user was likely to respond through emulating the reaction of carers.

Other techniques have been used to gain a better understanding of what is needed for new designs where there is a very intimate interface with the user. A European Commission-funded project, ENABLE, which evaluated the impact of assistive technology on people with dementia and their carers, placed a lot of emphasis on focus groups and other meetings with professional carers.[8] These sessions were very useful to explore solutions in an interactive manner. Another successful technique pioneered by researchers at Dundee University is the use of actors to provide a bridge between users and researchers.[9] The Dundee team explored the issue of falls in the elderly. They used actors to simulate situations where falls occur. These were useful both to get comments and feedback about situations and strategies and also as tests for the sensing technology they were developing.

Figure 124.6 Diagram of the tap developed to enable the water supply to be turned off without taking control away from the user.

The difficulty of behaviour monitoring

The main role of sensors in a smart home environment is to allow judgements to be made about user behaviour. Some aspects, such as whether someone has just come out of a toilet or not, are fairly easy to sense and make judgements about. Most aspects, however, are surprisingly difficult to judge, even for simple behaviours, where complications can arise from inevitable variations in the way in which different people act. For example, the work described above on bed-occupancy systems showed that the house cannot just turn the light off as soon as someone gets back into

bed. Users were found often to sit on the bed before getting back in, perhaps to remove slippers or dressing gown. If the lights went out straight away it caused some confusion, so a carefully judged delay was introduced to ensure that the user was fully back and settled in bed before turning off the lights. These may seem like minor points in the use of such technology but they can be major factors in the confidence that their users have in them and therefore their acceptance.

Bed-occupancy sensors would superficially seem to be very straightforward. A weight sensor can tell the difference between whether someone is in bed or out of it. However, such a sensor will also be activated by someone turning over in bed or moving from one side to the other. It also has to deal with situations that occur such as someone going to stand up from a bed and then not quite making it and falling back on to the bed before finally getting to their feet. The algorithms (simple computer programs) that use the raw sensor data and make conclusions and judgements based on it have to deal with all these variants of user behaviour (Figure 124.7). To ensure they are effective, a lot of raw data have to be collected so that all the variations can be seen. An effective algorithm can then be developed to deal with them.

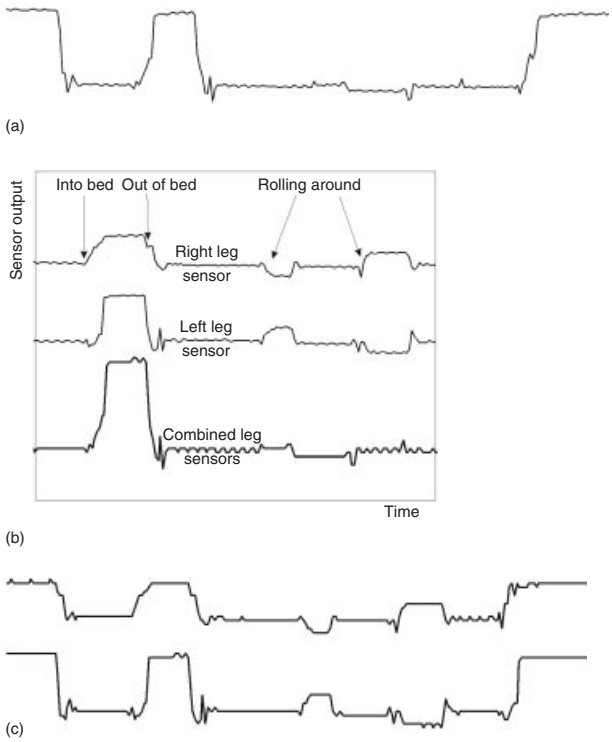

Figure 124.7 Raw data from a bed-occupancy sensor. Traces (a) and (b) show the output from the sensors fitted to both legs at the head end of the bed and trace (c) shows how the summed output can differentiate between getting in and out of bed and simply rolling around.

If the house gets it wrong with a bed-occupancy sensor, it is not so crucial. If it gets it wrong with, say, a gas cooker monitor, then the outcome could be much more serious. Making judgments about human behaviour based on simple sensor data is always going to be probabilistic. For example, with the gas cooker monitor developed for the Gloucester smart house, one of the sensors used was a simple infrared temperature sensor that was mounted at the side of the cooker and could detect the temperature of the pan or kettle. The data from the sensor were to be used to detect whether a pan had boiled dry or not, because then its outside temperature would increase very rapidly. However, users do not just leave a pan alone once it is in use on the cooker. They will very likely turn the gas up and down according to how the cooking was going. They may well move a pan around to different rings on the cooker. Such activities can make it very difficult to judge what is going on from the simple sensor data. A lot of cooking activities were monitored until it was felt that for about 80% of the time a pan could be reliably detected as having boiled dry. However, the other 20% of circumstances had to be dealt with in some way. It was decided to try and ensure that any errors were false positives. In other words, the cooker may on 20% of occasions turn off when it did not really need to do so. However, these false-positive activations proved to be irritating to users during evaluations. The exercise underlined the probabilistic nature of making judgements about user behaviour.

The level of errors could be reduced by incorporating information processing systems with learning capabilities, but it would still not reduce them to zero. Clearly, in these kinds of situations where there is potential danger there has to be some kind of backup. In the case of the cooker monitor, the device had a facility for shutting down the gas supply to the cooker if it continued to sense danger after responding to a danger signal. It also would call for assistance from outside the house in such situations. This is an important conclusion for smart house installations. Some aspects of the support that they provide are fairly safety critical. In these situations, it must be recognized that the house may make a false judgement about the user's behaviour and means for providing some kind of backup and a means for calling for outside assistance are essential.

The importance of communication with the user

It has already been stressed that communication with the user within the smart house is important. The smart house is an intelligent and autonomous care provider and, like any other carer, it needs to communicate with the person for whom it is caring. Voice communication is, of course, very flexible and has the advantage that it reflects the kind of interactions provided by a human carer, but it does have

some disadvantages. The communications that it provides are transient. If the user is forgetful, then a message that encourages them, for example, to take some medication may be registered but then forgotten a few minutes later. For users with severe memory problems, such as those with dementia, this problem is exacerbated. In addition, the very fact that voice messages are very anthropomorphic means that users may well treat them emotionally and get angry or irritated when prompted to do something.

When voice prompts were first proposed, some professional carers felt that this might not work for people with dementia because the person may well become very anxious by the use of disembodied voices, particularly people with conditions such as Lewy body disease where they tend to hallucinate and hear voices anyway. The other concern raised was that if the voice is recognized, the person with dementia may well think the owner of the voice is in the building and go looking for them. To try to address the first concern, the designers in the Gloucester smart house project made sure that any voice messages came from devices that normally had voices coming from them, such as the TV or radio. It was also decided to use a voice that was a warm anonymous one.

Most of the project's experience of voice prompts came from the use of a wander reminder for people with dementia. This device sits by the main door and if it detects someone in its vicinity at night-time it plays a voice prompt that says something like, 'It is still night-time, Joan. I should go back to bed' (Figure 124.8). If the user still goes out of the house, this is detected and an alarm is sent to a carer to alert them to the fact. Most of the users have been mild to moderate in their degree of dementia. The results have been very positive, with less wandering reported in most cases and no wandering in several. However, some carers have reported that the user just swears at the voice box!

Figure 124.8 A wander reminder fitted near an exit door.

The fact that the voice was disembodied does not seem to have been a problem. It would appear that people are used to voices coming out of little boxes from their lifetime experience of radio, tape recorders and so on, and it seems completely normal. Interestingly, there was some evidence of habituation to the message and the carer was encouraged to change the message from the anonymous one to recording a message of their own. One unexpected outcome from these changes was that it was reported that users seemed to respond better to a voice they recognized and trusted to give them good advice. All voice prompting systems subsequently used by the Bath team have used recorded voices from a close and trusted personal carer.

Other means for communication are being explored. As mentioned above, it would help to use messages that remain for a longer period for people with memory problems or who are forgetful. Simple hand-written text messages are often used by carers of people with dementia. For example, carers might use Post-Its around the house to remind the user not to touch certain appliances or to remind them to take medication and so on. Automated text messages on a small screen on the wall, which can be activated by the house in appropriate situations, are being explored. A further development of this idea that has been successfully tested is the use of simple pictures or graphics in addition to the written message. There is scope for providing these messages on the TV, where simple animation or even small video clips can be used.

Quality of life issues

It has been commented that smart home technology has primarily been used to support safety and security issues and not very much for other activities such as leisure.[10] The technology is ideal for monitoring activities such as cooker, fire and tap usage, to ensure appropriate temperatures and ventilation, to help prevent wandering or disorientation at night and so on. The impact that it has on quality of life is less clear and yet as far as the users themselves are concerned, it is maintenance of or improvement in their quality of life that is all important. Are there ways in which this technology can have an impact on quality of life?

Some work recently completed in the UK explored whether it is possible for smart home technology to have a more direct impact on quality of life.[11] The project, labelled INDEPENDENT, used grounded-theory qualitative techniques to tease out from interviews with people with dementia those aspects of their lives that had the most impact on their quality of life. A wish-list of 11 topics was compiled from this work, covering such aspects as reminiscence, relationship with family, access to music and social isolation. A number of topics were explored from the perspective of technologies that could be included in

a smart home environment. A useful example was the issue of reduction of social isolation, which was a key component of the wish-list. The study explored the use of video links between an elderly person and their family. It developed a very intuitive control interface based on the normal social etiquette of visiting someone. For example, the touch screen used for the user's control interface had a knock-on-the-door facility so that the elderly user could request a virtual visit with their family. The success of this work demonstrates that there is a lot of scope for these kinds of uses of technology, but it is in a complex area of human–technology interaction and to be successful it is important that it is led by an understanding of user needs rather than by the availability of technology. There is some indication from other work that even simple phone or video conference chats can provide a sense of social inclusion.[12] The often reported habit of TVs being left on in an otherwise empty home to provide a sense of social involvement gives an indication of the complex way in which people can interact with technology.

A key quality of life issue is, of course, that of independence and for the user to have a sense of being in control of their lives. It is for this reason that so much emphasis had been placed in the Gloucester smart house project on empowering the user and not letting the house take control away from them. Many issues that have an impact on quality of life are very personal to the individual. There can often be some barrier for a given individual that prevents them from doing something that may not seem that important to an outsider, such as being able to cook a simple meal for oneself. If such barriers can be identified and removed through the use of some technology, it could provide a big increase in their personal quality of life.

Links with the outside world

As was mentioned above, the major factor differentiating smart home technology from telecare systems is its ability to act autonomously. However, there is an important need for communication with the outside world. Already mentioned is the need for backup in the event of an emergency. The house needs channels of communication that can alert the carer and others to the fact that the house is not able to cope on its own. The Bath work, for example, used an SMS link to call for assistance. If the gas cooker monitor decided that there was still some danger despite it having turned off the cooker knobs, then it would shut down the gas supply and send a text message to the mobile phones of several carers, advising them to come and check and to turn the gas back on again. This system worked very well. Such links could be provided via landline phones and perhaps to a call centre. It would also be possible to send messages via a web server to appear on a remote monitor.

The external support described could provide details that would enable a care professional to make judgments about the impact of the technology. This is a difficult ethical area that needs much further exploration. On the one hand it might be seen to be useful for an OT just to check on how often one of her clients had used the toilet in case there was evidence of a urinary tract infection, for example. But is such personal intrusion really ethically acceptable? On the other hand, it would make sense for the house itself to flag a warning if it detected anomalous behaviour that might indicate excessive anxiety or to let OTs know if the gas cooker had to turn itself off more than 10 times in a week or if the refrigerator had not been opened for several days. Hence these links to the outside world seem to make sense if they can be preset to draw attention to some trend in the house, but it becomes much more ethically contentious when it is used as a tool to check and pry.

The importance of providing information to the outside world was underlined by the evaluations of smart installations where it was clear that there was an important need for carers, both professional and family, to know how the user was getting on. This was needed both to reassure the carer but also to let professional carers know whether adjustments they have made to the installation are effective or not. However, it is not clear just what kind of information needs to be provided. The raw sensor data are far too detailed to give carers a sense of how the user is doing, but a simple high-level indication, such as an okay/not-okay message, is not adequate. Carers require some interpretation of the raw data that can provide information about how they are sleeping and eating, whether there are any signs of anxiety or distress, and so on. Such interpretation is difficult to provide in an autonomous fashion. Some work has been completed exploring lifestyle monitoring. These techniques try to correlate sensor data with direct behaviour monitoring. They often use the norms of behaviour that have been learnt by the installation and which can then be used to check for changes. For example, simple movement around the living environment can be averaged to provide a measure of 'normal' movement. If there is a sudden increase in this activity it could be interpreted as a sign of increased restlessness or anxiety. This work is an important current research topic and so far has shown that human behaviour is actually very varied and difficult to pin down to norms of behaviour for a given individual.[13]

Having made judgements about how someone is getting on, the system then needs to present this to the carer. For professional carers, with perhaps many clients to oversee, this information needs to be presented in a very succinct fashion. It is likely that the system will alert carers to problems that have arisen rather than provide continuous data and then enable them to gain access and look at the more detailed information. Again, this is a key current research topic.

Experience of usage

A lot of work has been completed on experimental smart home systems, including much work in conjunction with elderly people. The key issue, however, is how users actually manage when using these kinds of installations in the longer term and experience of this usage is starting to accrue. As an illustration of the impact of the technology, some results from a year-long evaluation carried out in London are described below.[14] This work was carried out in a care home so that there was good backup in the event of any problems arising with technology that was still experimental.

The London installation was provided for a man with a moderate dementia, who had a Mini Mental State Examination (MMSE) score of 10 and whose OT assessment showed that he had a continence problem and a tendency to wander at night. A full set of support equipment was installed, to cover lighting, use of his cooker and taps, dealing with wandering, with sensors for movement, bed occupancy, use of equipment and with a complete voice prompt system using recorded messages from his daughter (his primary carer up to that point). Prior to turning on the installed support technology, the sensors were used to monitor his behaviour for the first month to provide some baseline data. The sensors showed that in addition to the problems highlighted by his initial OT assessment, he also had a major sleep problem. On average he was getting about $3\frac{1}{2}$ h sleep per night. He also seemed confused about where he was in the flat, often wandering around various rooms before getting to the toilet at night. Consequently, when the support equipment was configured, these observations were also taken into account. To support his incontinence, which primarily occurred at night, if he got out of bed the bedroom and toilet light were turned on. His daughter's recorded voice would inform him that the toilet light had been tuned on for him. When he finished in the toilet but did not go back to bed, his daughter's voice would encourage him to return to bed. This would be repeated at intervals three times and if he still wandered around the apartment the system would call for assistance from the night care staff. This simple intervention had a major impact on his life. The guidance to the toilet at night enabled him to become completely dry. The encouragement back to bed increased his sleep time up to around 6 h per night. He also had a system installed to discourage him from going out at night and this reduced these wandering incidents to around 20% of their previous level. Interviews with him and the care staff showed he was content and able to cope with most of his life.

This is just one example from a growing body of evidence that is showing the real impact of this technology. It is clear that to be effective it does need to be configured to suit the particular needs of a user, and this requirement complicates the configuration of installations. Such configurations need to be carried out by non-technical staff and so need to be simple to carry out, and make it essential that such staff receive good feedback about how their client is getting on. But the message that is developing is that these kinds of smart installations can enable users to be independent and safe.

The largest usage of smart homes for elderly people is in The Netherlands. Their Smart Home project has been under way for many years and involves many thousands of homes.[15] The installations are fairly basic and not really tailored to the needs of the individual, but they do include automatic lighting, monitoring of the outside door and a central home-locking facility. These approaches have recently been extended to explore their application to people with dementia.

Infrastructure needed for introduction

A lot of the work carried out so far on the use of smart homes for elderly and disabled people has been on very small-scale installations. They have been more akin to research projects to explore the potential of the technology. As evidence mounts that there are distinct personal benefits to the clients and as evidence also mounts as to the cost-effectiveness of the technology, there is an expectation that the technology can be rolled out to be used throughout the community. However, there are a number of infrastructural requirements that are needed to be satisfied before such a major step.

First, any such technology can only be used following an extensive assessment of the user's needs by a care professional, probably an OT. The OTs involved need to be knowledgeable about what assistive devices are available and their potential to provide support. In this way, they can match the needs of the individual to a prescription of the mix of technology that would best suit the client at that time.

Second, there needs to be a knowledgeable set of contractors, either employed by the company manufacturing the assistive technology or able to work for a number of different companies, to carry out the actual installations and configure them according to the results of the assessment process. As with environmental control technology, the commissioning process is complicated because it needs to involve a mix of technical people and OTs.

Third, there needs to be system of operational backup, as described above, in the event of emergencies arising. Such backup may well be provided by call centres, but there is no reason why this cannot be provided via care professionals directly or personal carers, particularly through web-based technology.

Fourth, there needs to be a well thought through system of technical maintenance that can be activated at very short notice. It is clear from the work of projects such as ENABLE

that users of sophisticated technology can become very anxious when it does not seem to be operating as they expect and they can quickly reject the technology if it appears to have gone wrong. Such backup would ideally be provided by manufacturers, but a front line of quick-reaction local technical support would probably be essential.

All the infrastructures described above would have to be in place before any large-scale installation of this technology. Similar facilities are also needed, of course, for telecare systems and these have been mostly put in place with remarkable efficiency over the last few years in the UK. Hence there is every reason to expect that such infrastructures can be put in place, particularly once the benefits of using this technology become more widely accepted.

Future trends

There is an important need for much more evaluation of smart home installations to get a better indication of the ways in which it supports users and indeed the ways in which it does not. Evidence is emerging as to those key features that are of most benefit, but much more work needs to be done in this area. In addition, the new support devices developed specifically for the elderly now need to be developed to a more mature state. As has been said, there are many items such as lighting controls that are already available off the shelf. Others such as cooker controllers and reminding devices are less so and need to achieve the same level of maturity. The main area where there is still a lot of work to do is in terms of the actual physical installations. The logic needed to control even a single home or apartment in a care home can be complex, particularly if it has to be able to be configured to suit a range of different users and deal with power cuts and computer crashes. If installations are to be plug-and-play, which they need to be, then the logic element that controls the system and provides the link to the outside world also needs to be plug-and-play. The software needed to configure a system for an individual needs to be developed so that it is very user friendly and can be used by care professionals.

For installations that are provided in care homes and sheltered housing schemes, then, the use of hard-wired communication buses is probably going to be the first choice. Such buses can provide excellent and well-proven reliability and they can provide the low power needed for many components of an installation. For builders of new housing schemes, it makes sense to install the bus cabling during the build, even if it is not being connected to support installations straight away, because it is very cheap to install at that time. For a retrofit installation, however, especially for those used in people's own homes, the use of hard-wired buses is much less suitable. It is very disruptive and time consuming to install and therefore expensive. For people who are likely to be anxious anyway, such as those with dementia, such installations can hardly be justified ethically. In these situations, radio-based buses or buses using mains wiring are much more appropriate. A number of radiofrequency buses are in use already and some modern developments such as the Ziggbee radio bus seem to have the right mix of range and bandwidth and power handling capabilities.

There is a need for further work on support devices and sensors, particularly those that can provide support that improves leisure and quality of life more generally. Finally, the technology to provide background behaviour monitoring, which has been a research topic for some years, is likely to provide added benefits. Such technologies should provide better judgements of complex behaviours that might reflect anxiety levels or specific issues such as falls. An extra topic that has been explored by several academic groups[16] is to see if the technology can be better tailored to the needs of the individual user by allowing it to learn the typical behaviour of the occupant. The house, through its sensors, can acquire a lot of information about the use of various appliances and the patterns of activity within the home. Once this information has been acquired, the house can adjust the settings according to how the user has been getting on. Such adaptive properties will also enable the installation to adapt to changes in the user's behaviour and learn the subtleties of an individual's requirements.

The installations that have been discussed throughout this chapter have been looking at home support technology that can act as a kind of extra care helper. However, the technology also has potential for linking in to other kinds of technological support and may well become integrated with them. For example, the burgeoning developments in telehealth technology could well use some of the same infrastructure as smart homes. If smart homes have appropriate links to the outside world and can sense user behaviour, then there is no reason why they cannot also report health issues resulting from the physiological and other sensors used by telehealth systems. There is also research going on looking at telerehabilitation, where home exercises and physiological responses can be remotely monitored in the same way as telehealth systems.

Conclusion

The application of smart home technology to support elderly and disabled people has developed rapidly over the last few years. Recent work has been much more user-led and aimed at supporting people with a wide variety of abilities, including those with dementia. Evidence is mounting that such systems can provide real benefits to the user and would also appear to have benefits from a cost point of view. There is still much work to be done, particularly with respect to improving quality of life and leisure activities.

However, provided that the relevant infrastructure can be put in place to support the technology, there is no reason why installations in both care homes and people's private homes cannot be a major feature of the support provided to elderly and disabled people in the very near future.

Key points

- The primary property that endows a house with the smart home label is its ability to support the user in an autonomous fashion.
- The main role of sensors in a smart home environment is to allow judgements to be made about user behaviour.
- The application of smart home technology to support elderly and disabled people has developed rapidly over the last few years, but more research is needed.

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CHAPTER 125

Skin disorders

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As the population continues to age, and the number of elderly persons increases, geriatric medicine. and more specifically geriatric dermatology. become an increasingly relevant specialty. With the progression of age, the incidence of dermatological diseases and disorders tend to increase.[1] This can be due to intrinsic ageing, skin ageing due to normal factors of maturity, which can be found in all of the ageing population, and extrinsic ageing, which is due to external factors such as smoking, environmental pollutants and exposure to UV light. Furthermore, factors that are more common in the elderly, such as decreased mobility, the increase of certain chronic diseases or an increase in a drug that can cause skin disorders as a side effect, all increase the risk of developing many dermatological diseases.[2]

Disorders which hinder vascular efficiency and immune response, such as diabetes mellitus, HIV, congestive heart failure and artherosclerosis, are all examples of diseases that can often cause skin disease or exacerbate already detrimental skin conditions. As people age, many changes take place in the ageing of their skin. Melanocytes decline, while photoageing causes density to double; Langerhans cells decrease in both density and responsiveness, and collagen decreases in density and in elastic papillary dermis tissue.[3]

The skin begins to thin and lose elasticity, resulting in wrinkling, irregular pigmentation, ease of tearing, neoplasia and several other like conditions. Photoageing accelerates and causes many conditions, such as actinic keratoses, wrinkling and telangiectasia, among other things. Likewise, nerves, circulation and sweat glands tend to begin a downward spiral in the path towards decreased ability to regulate temperature and skin sensitivity to burning. Nail health also weakens as the nails thin and become ridged and split and subcutaneous layers of fat atrophy and hypertrophy in their respective regions of the ageing body. Many of the common dermatological conditions developed in geriatric patients who are living in nursing homes or assisted living communities could be prevented with care given to the patient's medical history, medications, allergies, nutritional state, mental state, physical limitation and personal hygiene.[3]

Decubitus ulcers or 'pressure ulcers' are extremely common in the elderly, particularly in patients with illnesses that require them to be bedridden, immobile or in a wheelchair. These ulcers are often found over bony prominences, such as, but not limited to, elbows, ankles, heels and shoulders. Ischaemia and tissue damage result from the extended pressure on tissue for significant durations of time. As the pressure against the skin reduces blood flow to the region, it causes the tissue to die.[3–5]

Decubitus ulcers are organized in stages from Stage I, the first signs, to Stage IV, the worst in severity. The stages can be categorized as follows:

- *Stage I:* Changes in intact skin such as redness or blue or purple hues in darker pigmented skin and also temperature, sensation or consistency changes. The area may be painful or itchy with increased warmth or coolness in temperature and a spongy or firm consistency. Stage I ulcers usually disappear with relief of pressure and are fairly mild.
- *Stage II:* Necrosis in the epidermis and/or dermis accompanied by abrasions, blistering and other superficial ailments to the skin.
- *Stage III:* Deep necrosis to the subcutaneous layer of fat and/or fascia, perichondrium or periosteum. The underlying tendons, muscles, bone and cartilage are not exposed.
- *Stage IV:* Severe necrosis through fascia, exposing tendons, muscles, bone and/or cartilage. Decubitus ulcers of this stage and severity increase the risk for osteomyelitis.[3–5]

There are multiple causes of pressure ulcers, such as constant pressure, friction and shear. Continuous pressure restricts blood flow and deprives the tissue of oxygen whereas friction can damage the skin and thereby make it more likely to develop a pressure ulcer. Likewise, 'shearing', in which underlying bone moves in one direction while the skin moves in another, can cause cell

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wall and blood vessel tearing. This can happen even with slight movements, such as sliding down in bed. Pressure ulcers can result in severe and sometimes even life-threatening complications such as cellulitis that can also lead to meninigitis, bone (osteomyelitis) and joint infections (infectious or septic arthritis), cancer and sepsis.[3]

Diagnosis is usually possible simply by physical examination; however, blood tests are usually ordered to evaluate the patient's nutritional state and health and decide whether further testing is necessary. In cases of infection where antibiotics are to be used, Gram stain cultures should be taken. If the sores do not improve with treatment or are recurring, a biopsy may be done to check for cancer, fungi or abnormal bacteria.[3,4]

There are multiple treatment options, depending mainly on the stage and severity of the ulcers. First, for all decubitus ulcers, the pressure that caused the condition should be relieved. This can be done through the use of support surfaces such as special cushions or mattresses, rotating positions at 15 min intervals for wheelchair-bound patients and once every 2 h for bedridden patients. Other treatments include cleaning, with water and a mild soap for Stage I ulcers and saline solution for open sores, tissue debridement through surgical, mechanical, autolytic or enzymatic debridement, stage-appropriate dressing (such as no dressing for Stage I ulcers, hydrocolloid dressing for Stage II sores, etc.), hydrotherapy, oral antibiotics for infection, nutrition improvement and vitamin therapy such as vitamins A, C and K and zinc, which increase the speed of healing, and prescription of muscle relaxants to relieve muscle spasms. Other treatments include surgical repair and flap reconstruction and experimental treatments such as electrotherapy, hyerbaric oxygen and topical application of human growth factors.[3–5]

Prevention of decubitus ulcers is key. Proper nutrition, reduction of skin-to-skin contact, daily skin examinations for high-risk patients, reduction of pressure and shearing factors, proper hygiene, mobility improvement and introduction of repositioning schedules are all important methods of ulcer prevention. In long-term care facilities, such as hospices and nursing homes, decubitus ulcers are extremely common, generally estimated to have an incidence between 2.4 and 23%. New ulcers have an incidence of 12% over a 6 month period. Furthermore, it was found that there was an increasing number of discharged hospital patients with decubitus ulcers, likely due to the increased frailty and susceptibility to illness of the geriatric patients being treated in such a setting. The transfer of these patients into long-term care facilities explained up to 63% of the decubitus ulcers pre-existing admission.[3,5]

Eczematous dermatitis is a category that contains multiple types of eczema, including seborrheic dermatitis, gravitational eczema, autoeczematization eczema, psychogenic dermatitis, nummular eczema and asteatotic eczema, many of which are often found in the elderly population. Nummular eczema causes sometimes scaly coin-shaped lesions and pruritus, usually on the trunk, lower legs, upper extremities and dorsal surface of the hands. It is usually treated with topical steroids and emollients. Related infections are treated with antibiotics such as cephalexin or dicloxacillin.[3,6]

Stasis dermatitis is accompanied by varicose veins, pedal oedema and venous insufficiency and can cause an increased likelihood of developing cellulitis or ulceration. A 'flare-up' of stasis dermatitis can cause autosensitization dermatitis or an 'id' reaction, thereby causing a secondary distribution, acute and papulovesicular in nature. Seborrheic dermatitis involves erythematous and xerotic skin on the face, scalp, anogenital and trunk areas. The condition's severity may be influenced by the central nervous system as seborrheic dermatitis is found in greater incidence in those with quadriplegia and Parkinson's disease. *Pityrosporum ovale* is also thought to play a role in the illness. Seborrheic dermatitis should be treated with ciclopirox or ketoconazole applied topically daily. In cases of increased severity, oral ketoconazole or fluconazole may be used alongside anti-staphylococcal antibiotics when there is a secondary infection.[3,6]

Psychogenic dermatitides are comprised of multiple disorders including lichen simplex chronicus, neurotic excoriations (see Figure 125.1), delusions of parasitosis and prurigo nodularis. Scaly, red, sharply defined, lichenified plaques are a major signal of lichen simplex chronicus lesions and are often caused by patients who are atopic and overly concerned about pruritic lesions, and who rub and scratch an itchy area until the lichenification is seen. The condition is treated with water soaks, behaviour modification and steroids applied topically to the lesions, and also Kenalog injections in the scalp and clobetasol or fluocinonide solutions on lesions that are resistant.[3,6]

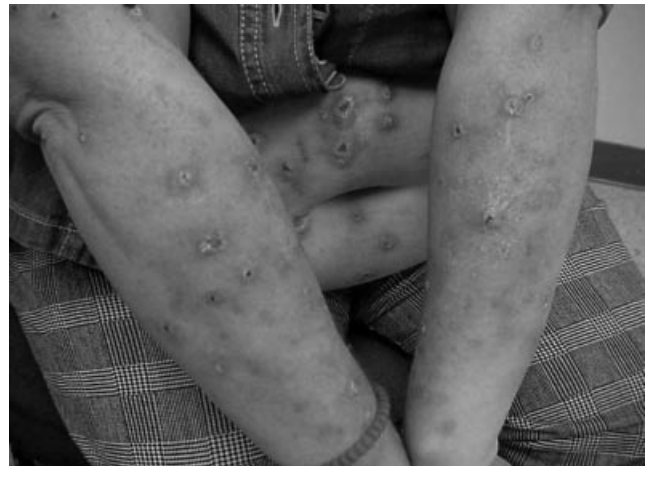

Figure 125.1 Neurotic excoriations of the arms and upper body. See plate section for a colour version of this image.

Prurigo nodularis is also a result of continual rubbing, scratching and picking and can be a result of stress. The nodules that characterize prurigo nodularis are erythematous and generally dispersed with keratotic nodules on the extremities. Treatment includes the topical application of triamcinolone acetonide or another corticosteroid or even a stronger steroid such as betamethasone. Alternative treatments include corticosteroid tape.

Similar treatments are applied for excoriated papules in post-inflammatory scarring at different points of healing. These neurotic excoriations may be found in patients whose condition does not fall into a normal pattern and who use their skin as a tool on which to release stress. Psychotherapeutic treatment plans are recommended by Truensgaard.[3,7] This can include strengthening the relationship between the patient and doctor, introducing alternative tactics to avoid scratching, identifying and reducing causes of stress and identifying triggers.

Delusion of parasitosis is a symptom of psychosis in which the patient complains of the feeling of parasites crawling on them when there is no evidence to support this as being true. Related factors include nutritional deficiency, arteriosclerosis, toxins and drug addiction. Depressive patients are usually treated with fluoxetine or doxepin, alprazolam or hydroxyzine for anxiety and pimozide or haloperidol for delusions. Alternative treatments may be used alongside anti-psychotics. Zyprexa may also be used.[3,6,7]

Fungal infections are also commonplace in the elderly community. These can include candidiasis, tinea pedis, tinea cruris and onychomycosis. *Candida* thrives in warm, moist environments where there is skin-to-skin contact and is a dispersed, bright red eruption with leaking pustules. When examined through a microscope, one can observe spores and pseudohyphae. Candidiasis is often associated with diabetes and oral antibiotic therapies. Treatment usually involves cold compress application with Burrow's solution, topical application of antifungal creams such as econazole or miconazole and, after the eruption is cleared, absorbent powder.[3]

Tinea pedis, also known as 'athlete's foot', infects the foot, appearing as erythematous dermatitis with a scaly and macerated presentation and, in some cases, ulceration and fissures. It can also appear alongside a secondary bacterial infection. Tinea pedis can be prevented with topical applications of benzoyl peroxide post-bathing and the wearing of shower shoes. It is treated with an imidazole such as clotrimazole, econazole or ketoconazole or an allylamine. Resistant infections may be treated with oral itraconazole, fluconazole or terbinafine.[3,8,9]

Tinea cruris, also known as 'jock itch', affects the groin region, in an erythematous, scaly, itchy eruption and is most commonly seen in males. Reduction of moisture is integral to the treatment of the condition and an antifungal cream is usually applied topically as treatment. Severe infection may be treated with oral antifungals. A betamethasone dipropionate–clotrimazole mixture may also be applied topically to areas of inflammation for limited periods of time.[3,9]

Almost half of patients exceeding 70 years of age suffer from onychomycosis, usually caused by tinea unguium, *Candida* or moulds. Symptoms include pain, ulcerations within the nail bed and secondary bacterial infection. The most frequently seen form of onychomycosis, distal and lateral subungual onychomycosis (DLSO), often appears first as just a white spot on a nail that then darkens, causing the nail to become thick and crack. Treatment usually involves debridement, systemic treatment, topical treatment, benzoyl peroxide washes and improvement of hygiene.[3,10]

As malnourishment and malnutrition, disease and trauma, among other things, cause changes and weakness in the skin's makeup, skin infections become a common occurrence in the elderly. Likewise, some forms of dermatitis and insect bites and stings can reduce the skin's natural resistance and thereby allow entrance to infections such as *Staphylococcus* and *Streptococcus*. These strains can cause impetigo in bullous or non-bullous form and, although it is often self-limiting, treatment should still be applied owing to the risk of complications such as post-streptococcal glomerulonephritis.[3,11]

The bullous form of impetigo is a result of the site of the infection producing epidermolytic toxins and is defined by bullae containing cloudy or clear fluid that can burst and leave a hyperpigmented rim surrounding the lesions and honey-coloured crusted exudates. The non-bullous form of impetigo presents as pustules that can rupture, leaving a red, swollen base and a yellowish crust. This comprises 10% of impetigo and is of some resemblance to the reaction to poison ivy.[3,12]

There may be some 'honey crusting' inside the bulla. Usually before impetigo, *Staphylococcus aureus* invades the nose and affects the areas around the nose and mouth and also on the limbs. Group A beta-haemolytic streptococci (GAS) occur on the intact skin and after abrasion, cut or other trauma, they enter the wound and cause infection. Treatment is usually with oral antibiotics such as cephalexin, dicloxacillin or cloxacillin or a 5 day course of azithromycin at 500 mg for the first day and half that amount on subsequent days. Mupirocin is also applied topically three times per day for the lesions.[3,11,12]

Parasitic diseases such as scabies and pediculosis are common in the elderly. Head, body and pubic lice, accompanied by pruritic papules, can be transmitted through direct contact with the infected person. Diagnosis is often carried out through examination and finding of nits. Lice are initially treated with permethrin and combing of nits. In

persistent cases, treatment with malathion lotion or lindane may be given.

Scabies is characterized by burrows alongside papules and vesicles. It is diagnosed through the analysis of skin scrapings and finding of ova, mites or faeces. Scabies is often found in the male genitalia or female areolas of the nipples and can also be seen on the scalp. In keratotic scabies, thousands of mites infest the skin, a considerably larger number than the average 3–50 mites. Treatment involves oral ivermectin in 12 mg doses, one week apart, and thorough cleaning of fomites.[3,13,14]

Herpes zoster or 'shingles' is a common affliction in the geriatric community, often waiting in a dormant stage within cutaneous neurons for significant periods of time and reappearing in times where the immune system is weak or the patient is undergoing significant stress. Herpes zoster usually manifests with pruritus, burning or pain before an eruption and, in some cases, lymphadenopathy. Other symptoms may include fever, lethargy or headaches. Shingles is characterized by clusters of vesicles containing clear fluid that quickly become pyogenic and later dry up and crust over. Related pain ranges from mild to severe and can last even years after the physical signs of the condition have faded.

Herpes zoster is managed with prevention by vaccination against varicella zoster. If the condition has already been contracted then antiviral therapy is begun immediately using acyclovir, valacyclovir or another similar medication, preferably within 72 h of the appearance of the first vesicle. Symptoms are managed with bed rest, opioid analgesics, capsaicin cream, NSAIDs, tricyclic antidepressants and, in severe cases of pain, nerve blocks. Ophthalmologist referral may be necessary when there the trigeminal nerve is affected.[3,15]

Another condition seen in the geriatric population is molluscum contagiosum, characterized by dome-shaped, umbilicated papules, and can be transferred by direct skin contact. The condition is more common in HIV patients, which has now become more of a chronic disease and in those who are immunocompromised by a variety of diseases. Treatment usually involves 5% imiquimod cream applied topically, but may also include electrodesiccation, curettage, laser surgery or cryotherapy. It is not uncommon for molluscum contagiosum to be misdiagnosed as warts, sebaceous hyperplasia or skin cancer.

Nutritional deficiencies often play a large role in dermatological disorders within the geriatric population. Scurvy is a result of vitamin C deficiency. Gingival and dermatological haemorrhages and the formation of hyperkeratotic papules surrounding hair follicles are also commonly seen. Pellagra is caused by vitamin B deficiency or niacin deficiency and can cause the skin to develop extreme photosensitivity. Dietary improvement and vitamin supplementation should be utilized as treatment for these deficiencies and also a thorough analysis of underlying and pre-existing causes and illnesses that may play a role in malnourishment.

Vascular disorders such as chronic venous insufficiency can be inherited in addition to being caused and exacerbated by continuous standing or venous thrombosis. Symptoms include oedema, varicose veins, pigment discoloration and venous ulcers. Leg elevation, support stockings, exercise, corticosteroids and surgery are used in treating vascular disorders.[3]

Tumours, both benign and malignant, are a common dermatological finding in the elderly. Benign tumours include leukoplakia, seborrheic keratosis, actinic keratosis, cherry angioma and keratoacanthoma. Malignant tumours include basal cell carcinoma (see Figure 125.2), squamous cell carcinoma and melanoma. Cherry angiomas are a primarily cosmetic concern and are treated with lasers or electrocoagulation. Leukoplakia is found on mucosal surfaces and is related to the use of tobacco and alcohol. A premalignant neoplasm, leukoplakia can turn into an invasive carcinoma. Leukoplakia is treated with topical application of 5-fluorouracil and electro- or cryosurgery. In severe cases, excision may be necessary.[3,16]

Seborrheic keratoses are frequently found in geriatric patients as dark papules 'stuck' on to the skin. In dark or irregular lesions, a biopsy should be taken to eliminate the possibility of melanoma and treatment should include electrocautery or cryosurgery. Actinic keratosis may be accompanied by a burning and stinging sensation and a red–brown papule. High-risk individuals with multiple actinic keratoses have progression rates to squamous cell carcinoma as high as 30% over three years. Treatment options include cryosurgery, electrodesiccation, curettage, blue light therapy and topical 5-fluorouracil.[17]

Basal cell carcinoma (BCC) is the most frequently found malignant tumour in humans and can appear superficial, nodular-ulcerative or morpheaform. Nodular-ulcerative

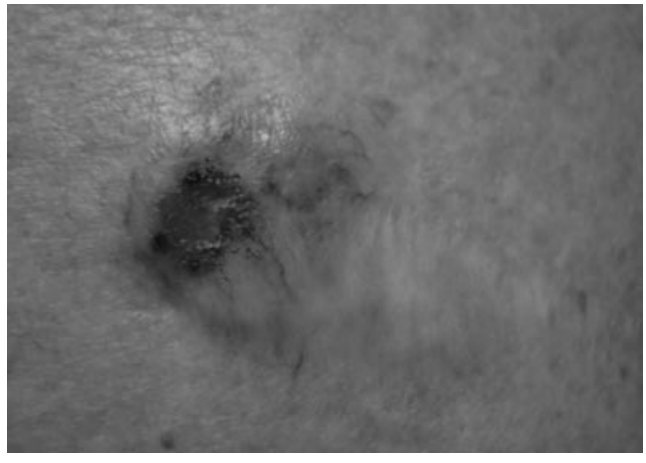

Figure 125.2 Basal cell carcinoma. See plate section for a colour version of this image.

BCC appears red with telangiectasia. Morpheaform lesions tend to have yellow–whitish plaque and superficial BCC has swollen, hyperpigmented lesions. UV exposure and ionizing radiation therapy are major risk factors for BCC. Treatment varies according to the region affected and severity of the BCC and can include excision, electrosurgery, radiation and Mohs micrographic surgery.

Squamous cell carcinoma (SCC) is a result of human papillomavirus (HPV) or UV exposure, the latter being the more frequently seen cause in the elderly. SCC often manifests as scaly, defined plaque and ranges from soft and poorly defined to firm and clearly defined. SCC is generally treated through the use of cryotherapy and 5-fluorouracil applied *in situ*. In severe cases, the lesion may be excised.

Malignant melanoma is occurring with increased incidence, especially with rising age. Types include superficial spreading melanoma, lentigo maligna, nodular melanoma and acral lentiginous melanoma. Superficial spreading melanoma occurs in about 70–80% of the patients with melanoma. Lentigo maligna is most often found in Caucasians who have exposed themselves to large amounts of sun and is asymmetric with abnormal borders. Acral lentiginous melanoma is found more often in individuals with darker shades of skin and can be found in the hands, feet and even the nails. The lesion tends to appear as a brown macule and slowly becomes larger over time.[3,17]

When assessing a prognosis for those who have melanoma, one must measure the depth. Those with a depth of less than 1 mm have a 5 year survival rate of >85% or more whereas those who have melanoma >4 mm in depth have a 5 year survival rate of <50%. With melanoma diagnosis, a biopsy is necessary. A punch biopsy should be used to measure the depth adequately. Melanomas are treated with lesion excision in the subcutaneous fat, close observation, investigation of spread to the lymph nodes and screening of immediate relatives.[3]

Purpura is a result of thrombocytopenia, vascular defect, drug reaction, trauma or platelet abnormality. Due to the loss of blood vessels and elasticity in the skin along with loss of fat and dermal collagen, the skin tends to thin and become increasingly exposed to external trauma. A large proportion of the geriatric population is taking medication which cause thrombocytopenia. Recommended treatment includes identification of initial cause, prescription of oral glucocorticoids and immunoglobulins and platelet transfusions as needed.[18]

A common dermatological disorder within the geriatric population that is not often realized by many to be 'dermatological' in nature is hair loss. Although hair does tend to thin and reduce with age, many in the geriatric population, men and women alike, find themselves with mild to severe hair loss and, as a result, a decreased sense of confidence and self-value. Conditions such as androgenetic alopecia, cicatricial alopecia and alopecia areata can signal an entrance to a stage in life in which one's physical strength and beauty have diminished and mortality and the passage of time are an all too real concern. There are a number of treatments for each of the conditions and also several others that are still in the experimental stage to help with this transition.[19]

Geriatric dermatology is a very broad topic covering many diseases and conditions. This chapter has outlined key, commonly seen illnesses from various categories to give brief snapshots of the bigger picture. However, when considering the depth and breadth of the field that is geriatric dermatology, one must examine multiple facets, from the physical to psychological, and also the underlying factors, including poor hygiene, caregiver neglect, drug reaction or a pre-existing medical cause. Although it is a field that primarily involves the skin, deeper investigation shows that one's dermatological condition is not a shallow field made up only of rashes, xerosis or eczema, but a canvas that can also showcase one's physical state from an internal standpoint, whether it be a decline in health due to diabetes mellitus, HIV or heart failure.

Key points

- Skin disorders increase with ageing.
- Shingles is a common affliction in older persons.
- High-risk patients with multiple actinic keratoses may progress to squamous cell carcinoma.
- Dermatological conditions showcase one's underlying physical status.

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CHAPTER 126

The prevention and management of pressure ulcers

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Pressure ulcers are the visible evidence of pathological changes in the blood supply to dermal tissues. Pressure ulcers are rare, affecting only about 0.5% of the total population. The distribution is clustered into two groups, peaking once in younger, mostly neurologically impaired persons, and again in older persons. The cluster in the geriatric population accounts for about 70% of all pressure ulcers.[1]

The chief cause has historically been attributed solely to pressure or force per unit area, applied to susceptible tissues. In this view, external pressure is viewed as the chief cause in the development of a pressure ulcer. Although it is recognized that other contributing or confounding factors are also associated with development of a pressure ulcer, these factors are often downplayed or disregarded.[2] Pressure is concentrated wherever weight-bearing points come in contact with surfaces. Muscle tissue, subcutaneous fat and dermal tissue are differentially affected in that order. The differential effect of pressure on the tissue layers suggests that injury occurs first in muscle before changes are observed in the skin, the so-called deep tissue injury. Pressure ulcers are classified in stages defined by the visible layers of tissue damaged from the surface towards the bone. Current research clearly demonstrates that a bottom-to-top pathogenesis is commonplace. In many cases, the changes visible at the surface of the tissue are minor compared with the damage seen at the deepest layers of tissue. This differential tissue susceptibility suggests that a number of factors are involved in the development of pressure ulcers, including the type of pressure load and biochemical changes in the tissue due to reperfusion injury or tissue compression.[2]

Provocative research into human skin blood flow may shed some light on the development of pressure ulcers. Skin blood flow before and during surgery was monitored in subjects selected because of lengthy abdominal or spine surgical procedures.[3] Pressure ulcers developed in 36% of these subjects. Contrary to the hypothesis that prolonged pressure reduces skin blood flow, an increase in skin blood flow was observed in most subjects during surgery. However, in the persons who developed a pressure ulcer, the skin blood flow decreased to half of the preoperative levels, whereas skin blood flow in persons who did not develop a pressure ulcer increased to 500% of maximum baseline value. These data suggest that individual tissue response is more important than externally applied pressure.

Other studies have suggested that sacral skin blood flow is higher than blood flow over the gluteus maximus,[4] and that a decrease in skin blood flow may be more serious in the sacral area than in other areas. Sacral pressure ulcers are common, but gluteal pressure ulcers are rare. The neural response to cold stimulation produces differences in skin blood flow among older subjects who do or do not develop pressure ulcers. There was a positive correlation between the blood flow response time over the greater trochanter and the development of pressure ulcers.[5]

The measure of skin blood flow is technically difficult, with a high degree of variability. However, these data suggest that individual factors may act in concert with external pressure in the development of pressure ulcers.

About 95% of pressure ulcers occur in the lower part of the body. The sacral and coccygeal areas, ischial tuberosities and greater trochanteric areas account for the majority of pressure ulcer sites.[6] The sacrum is the most frequent site (36% of ulcers). The heel is the next most common site (30%), with other body areas each accounting for about 6% of pressure ulcers.[7,8]

Clinical staging of pressure ulcers

Several differing scales have been proposed for assessing the severity of pressure ulcers. The most common staging, recommended by the National Pressure Ulcer Task Force and nursing home guidelines, derives from a modification of the Shea Scale.[9] Under this schematic, pressure ulcers

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

are divided into four clinical stages. The staging system for pressure ulcers relies on a description of the depth of the wound. An evolutionary process in the understanding of tissue injury has led to an expansion into six stages in the USA and recent attempts to reach consensus on clinical description (see Table 126.1).

This staging system for pressure ulcers has several limitations. The primary difficulty lies in the inability to distinguish progression between stages. Pressure ulcers do not progress absolutely through Stage I to Stage IV, but may appear to develop from 'the inside out' as a result of the initial injury. Healing from Stage IV does not progress through Stage III to Stage I, but rather heals by contraction and scar tissue formation. Since pressure ulcers heal by contraction and scar formation, 'reverse staging' is inaccurate in assessing healing. Thus, improvement or deterioration between clinical stages cannot be determined. Clinical staging is inaccurate unless all eschar is removed, since the staging system only reflects depth of the ulcer.

No single measure of wound characteristics has been useful in measuring healing.[10] Several indexes have been proposed, but lack validation. The Pressure Ulcer Status for Healing (PUSH) tool was developed and validated to measure healing of pressure ulcers. The tool measures three components, size, exudate amount and tissue type, to arrive at a numerical score for ulcer status. In clinical development and validation studies, the PUSH tool adequately assesses ulcer status and is sensitive to change over time.[11,12] In the USA, the PUSH tool is incorporated into the Minimum Data Set version 3.0. The PUSH tool is shown in Figure 126.1.

Prevention of pressure ulcers

Despite considerable attention to and research on the prevention of pressure ulcers, the prevalence and incidence of pressure ulcers have changed little over the last decade,[13] even in the face of improved application of prevention modalities. The incidence of pressure ulcers as a primary diagnosis in hospital settings varied from 7.0 to 8.3 per 100 000 population but did not change from 1987 to 2000.[14] In another hospital setting, the point prevalence of Stage II or higher pressure ulcers was 33.3% in 2002 and 28.2% in 2004. The point prevalence decreased in surgical care units (from 26.8 to 17.3%) and increased in medical care units (from 23.6 to 26.7%), despite demonstrated increases in prevention measures.[15] Similar stability has been observed in other populations, indicating that reducing pressure ulcer prevalence rates remains a challenge.

Recognizing patients at risk

Comorbid conditions, especially those resulting in immobility or paralysis or reduced tissue perfusion, such as hypoxia due to respiratory or cardiac disease, greatly increase the risk of developing pressure ulcers. In theory, persons who are at high risk for developing pressure ulcers can be identified and increased effort can be directed to preventing ulcers in these persons.

Considerable effort has been directed towards risk assessment. The classical risk assessment scale is the Norton Score, developed in 1962 and still widely used. Patients are classified using five risk factors graded from one to four. Scores range from 5 to 20, with higher scores indicating lower risk. In the initial study, 48% of patients who scored less than 12 developed pressure ulcers, compared with only 5% of those who scored above 18. The generally accepted at-risk score is 14 or less and patients with scores below 12 are at particularly high risk. The Norton score has been expanded into the Waterlow Scale in the UK.

A commonly used risk assessment instrument in the USA is the Braden Scale. This instrument assesses six items: sensory perception, moisture exposure, physical activity, mobility, nutrition and friction/shear force. Each item is ranked from one (least favourable) to three or four (most favourable) for a maximum total score of 23. A score of 16 or less indicates a high risk. A comparison of the instruments is shown in Table 126.2.

Both the Norton Score and the Braden Scale have good sensitivity (73–92 and 83–100%, respectively) and specificity (61–94 and 64–77%, respectively), but both have poor positive predictive value (around 37% when the pressure ulcer incidence is 20%). In populations with an incidence of pressure ulcers less than 20%, such as nursing homes, the same sensitivity and specificity would produce a positive predictive value of 2%. The Norton Score and Braden Scale show a 0.73 kappa statistic agreement among at-risk patients, with the Norton Score tending to classify patients as at risk when the Braden Scale classified them as not at risk. The net effect of poor positive predictive value means that many patients who will not develop pressure ulcers will receive expensive and unnecessary treatment. Risk factor assessment illustrates the concept that individual patient factors interact with pressure in the aetiology of pressure ulcers.

A systematic review of 33 clinical trials of risk assessment found no decrease in pressure ulcer incidence that could be attributed to the use of an assessment scale.[16] However, the use of a risk assessment scale tended to increase the intensity of prevention interventions. The Braden Scale offered the best balance between sensitivity and specificity and the best risk estimate compared with other scales. In this review, both the Norton Score and Braden Scale were observed to be more accurate in predicting pressure ulcer risk than nurses' clinical judgement. These results agree with other systematic reviews showing no evidence that risk assessment scales are independently effective for pressure ulcer prevention.[17,18]

Table 126.1 Clinical staging of pressure ulcers.[a]

Stage	NPUAP	EPUAP
Stage/Category I	Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its colour may differ from the surrounding area	Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its colour may differ from the surrounding area. The area may be painful, firm, soft, warmer or cooler compared with adjacent tissue. Category I may be difficult to detect in individuals with dark skin tones. May indicate 'at risk' persons
Stage/Category II	Partial thickness loss of dermis presenting as a shallow, open ulcer with a red–pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled blister	Partial thickness loss of dermis presenting as a shallow open ulcer with a red–pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanginous filled blister. Presents as a shiny or dry, shallow ulcer without slough or bruising. This category should not be used to describe skin tears, tape burns, incontinence-associated dermatitis, maceration or excoriation
Stage/Category III	Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunnelling	Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunnelling. The depth of a Stage/Category III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and Stage/Category III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Stage/Category III pressure ulcers. Bone/tendon is not visible or directly palpable
Stage/Category IV	Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunnelling	Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often includes undermining and tunnelling. The depth of a Stage/Category IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and these ulcers can be shallow. Stage/Category IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon or joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable
Suspected deep tissue injury (used in USA)	Purple or maroon localized area of discoloured intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared with adjacent tissue	Purple or maroon localized area of discoloured intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler compared with adjacent tissue. Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may further evolve and become covered by thin eschar. Evolution may be rapid, exposing additional layers of tissue even with optimal treatment
Unstageable (used in USA)	Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, grey, green or brown) and/or eschar (tan, brown or black) in the wound bed	Full thickness tissue loss in which actual depth of the ulcer is completely obscured by slough (yellow, tan, grey, green or brown) and/or eschar (tan, brown or black) in the wound bed. Until enough slough and/or eschar are removed to expose the base of the wound, the true depth cannot be determined; but it will be either a Stage/Category III or IV. Stable (dry, adherent, intact without erythema or fluctuance) eschar on the heels serves as 'the body's natural (biological) cover' and should not be removed

[a]A comparison of the National Pressure Ulcer Advisory Panel (NPUAP) and the European Pressure Ulcer Advisory Panel (EPUAP) clinical staging systems. In the USA, the convention is to use the term 'Stage' whereas in Europe the term 'Category' is preferred.
Adapted from European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel. *Prevention and Treatment of Pressure Ulcers: Quick Reference Guide*. National Pressure Ulcer Advisory Panel, Washington, DC, 2009.

Patient Initials:_____ Date:

DIRECTIONS: Observe and measure the pressure ulcer. Categorize the ulcer with respect to surface area, exudate, and type of wound tissue. Record a sub-score for each of these ulcer characteristics. Add the sub-scores to obtain the total score. A comparison of total scores measured over time provides an indication of the improvement or deterioration in pressure ulcer healing.

	0 0 cm^2	**1** < 0.3 cm^2	**2** 0.3-0.6 cm^2	**3** 0.7-1.0 cm^2	**4** 1.1-2.0 cm^2	**5** 2.1-3.0 cm^2	
Length x Width		**6** 3.1- 4.0 cm^2	**7** 4.1-8.0 cm^2	**8** 8.1-12.0 cm^2	**9** 12.1-24.0 cm^2	**10** >24.0 cm^2	**Sub-score**
Exudate Amount	**0** None	**1** Light	**2** Moderate	**3** Heavy			**Sub-score**
Tissue Type	**0** Closed	**1** Epithelial Tissue	**2** Granulation Tissue	**3** Slough	**4** Necrotic Tissue		**Sub-score**
							Total score

Length x Width: Measure the greatest length (head to toe) and the greatest width (side to side) using a centimeter ruler. Multiply these two measurements (length times width) to obtain an estimate of surface area in square centimeters (cm^2). Caveat: Do not guess! Always use a centimeter ruler and always use the same method each time the ulcer is measured.
Exudate Amount: Estimate the amount of exudate (drainage) present after removal of the dressing and before applying any topical agent to the ulcer. Estimate the exudate (drainage) as none, light, moderate, or heavy.
Tissue Type: This refers to the types of tissue that are present in the wound (ulcer) bed. Score as a "4" if there is any necrotic tissue present. Score as a "3" if there is any amount of slough present and necrotic tissue is absent. Score as a "2" if the wound is clean and contains granulation tissue. A superficial wound that is reepithelializing is scored as a "1". When the wound is closed, score as a "0".

4 - Necrotic Tissue (Eschar): black, brown, or tan tissue that adheres firmly to the wound bed or ulcer edges and may be either firmer or softer than surrounding skin.
3 - Slough: yellow or white tissue that adheres to the ulcer bed in strings or thick clumps, or is mucinous.
2 - Granulation Tissue: pink or beefy red tissue with a shiny, moist, granular appearance.
1 - Epithelial Tissue: for superficial ulcers, new pink or shiny tissue (skin) that grows in from the edges or as islands on the ulcer surface.
0 - Closed/Resurfaced: the wound is completely covered with epithelium (new skin).

Figure 126.1 PUSH Tool Version 3.0. Adapted from Stotts *et al.*[12]

Whether prevention measures should begin as soon as the person has a high risk assessment score or after the development of non-blanchable erythema (a Stage I pressure ulcer) was observed in a randomized controlled trial. All subjects were observed daily for incident Stage I pressure ulcers and a Braden risk assessment scale was obtained every 3 days. Subjects received identical prevention measures, including turning every 4 h in combination with either polyethylene–urethane mattress or an alternating pressure air mattress. In the experimental group, the intervention was started when a Stage I pressure ulcer appeared. In the control group, intervention began when the Braden Score was 17 or less. In the experimental group, 16% of patients received preventive measures, whereas 32% of the risk score assessment group received preventative measures. The pressure ulcer incidence (Stages II–IV) was not significantly different between the experimental group (6.8%) and control group (6.7%). Significantly fewer patients needed preventive measures when preventative measures were postponed until a Stage I pressure ulcer was present, but those patients did not develop more pressure ulcers than patients who received prevention measures based on the standard risk assessment method.[19]

Relieving pressure, friction and shear force

In those patients at risk, the first preventive action targets reduction in the effect of pressure, friction and shear forces. The most commonly recommended method for reducing pressure is frequent turning and positioning. A 2 h turning schedule for spinal injury patients was deduced empirically in 1946.[20] The exact interval for optimal turning for the prevention of pressure ulcers is unknown, but the interval may be shortened or lengthened by host factors. In healthy older

Table 126.2 Comparison of risk assessment scales.

Variable	Norton	Braden	Waterlow
Mobility	×[a]	×	×
Moisture exposure	×	×	×
Physical activity	×	×	
General condition	×		×
Nutrition		×	
Appetite			×
Friction/Shear force		×	
Sensory perception		×	
Mental status	×		
Skin type			×
Medication			×
Weight			×
Age			×
Gender			×
Other (e.g. disease)			×

[a] × = Scale contains this item.

volunteers, intervals of 1–1.5 h rather than the traditional 2 h schedule were required to prevent skin erythema on a standard mattress.[21]

Turning the patient to relieve pressure may be difficult to achieve despite best nursing efforts and is very costly. Despite common-sense approaches to turning, positioning and improving passive activity, no published data support the view that pressure ulcers can be completely prevented by passive positioning.[22,23]

Pressure-reducing surfaces

Because of the limitations and cost of turning schedules, a number of pressure-reducing devices have been developed for prevention of pressure injury. The theoretical goal is to reduce tissue pressure below a capillary closing pressure of 32 mmHg.

Devices can be defined as pressure-relieving (consistently reducing interface pressure below 32 mmHg) or pressure-reducing (less than standard support surfaces, but not below 32 mmHg). The majority of devices are pressure-reducing. Pressure-reducing devices can be further classified as static or dynamic. Static surfaces are stationary and attempt to distribute local pressure over a larger body surface. Examples include foam mattresses and devices filled with water, gel or air. Dynamic devices use a power source to produce air currents and promote uniform pressure distribution over body surfaces. Examples include alternating pressure pads, air suspension devices and air-fluidized surfaces. When compared with a standard hospital mattress, a number of pressure-reducing devices lower the incidence of pressure ulcers by about 60%.[24]

The capability of devices to reduce pressure differs depending on body site. Sacral pressure reduction can be achieved in healthy volunteers by several devices. Three dynamic air support systems lower pressure at the trochanter compared with a conventional mattress. However, no device reduced pressure over the trochanter to physiological levels.[25,26] Few currently marketed devices, including air-fluidized beds, will consistently reduce heel pressure below the minimum capillary pressure.[27] It is important to note that although some dynamic air mattresses and flotation systems can reduce pressure to near physiological levels, all benefit is lost if the head of the bed is elevated to 30°, such as for tube feedings.[28]

Comparison between different devices to reduce pressure remains confusing. No statistically significant difference has been found between alternating pressure, constant low pressure, foam overlays, silicone overlays or air- or water-filled devices.[24] Therefore, a pressure-reducing device should be selected on the basis of cost and ease of use. The cost of pressure-reducing devices varies considerably, with air-fluidized and low-air-loss systems the most expensive and static support overlays the least expensive. Dynamic devices are often noisy and disturbing to patients. Mechanical difficulties are frequent with all types of devices. The data also demonstrate that pressure ulcers develop in some patients in spite of the use of pressure-reducing devices. Overall, the data suggest that patients likely to develop a pressure ulcer should be treated with a pressure-reducing device, although no one device appears to be superior to another.

Combinations of turning/positioning and pressure-reducing surfaces

When a pressure-reducing device is combined with turning and positioning, the effective interval for turning may be reduced. In a randomized controlled trial in high-risk nursing home residents, four different turning schedules were used. Subjects were either turned every 2 h on a standard institutional mattress, or turned every 3 h on a standard institutional mattress, or turned every 4 h on a viscoelastic foam mattress, or turned every 6 h on a viscoelastic foam mattress. The incidence of non-blanchable erythema (a Stage I pressure ulcer) was not different between the groups (35–38%). However, the incidence of a Stage II and higher pressure ulcers was 3% in the 4 h turning interval group, compared with incidence figures in the other groups varying between 14 and 24%. Turning every 4 h on a viscoelastic foam mattress resulted in a significant reduction in the number of higher stage pressure ulcer lesions and suggests that less frequent turning in combination with a pressure-reducing mattress is effective and feasible.[29,30]

The effect of different body positions was evaluated in another randomized controlled trial. Subjects who had non-blanchable erythema (Stage I pressure ulcer) were assigned to either of two groups. In the experimental group, patients

were repositioned 2 h in a lateral position alternating with 4 h in a supine position. In the control group, patients were repositioned every 4 h. Both groups received a pressure-reducing mattress. The sitting protocol was identical in both groups. It was found that 16% of subjects in the experimental group and 21% of subjects in the control group ($p = 0.40$) developed an incident Stage II–IV pressure ulcer. Neither the severity, location nor time to development of the pressure ulcers differed between groups. It was difficult to maintain subjects in a lateral position between the turning intervals. The authors concluded that more frequent repositioning on a pressure-reducing mattress does not necessarily lead to fewer pressure ulcer lesions and consequently cannot be considered as a more effective preventive measure.[31] Other trials have found similarly high incidence despite various interventions.[32–34]

A systematic review of published prevention strategies for prevention of pressure ulcers up to June 2006 found only 59 randomized controlled trials, 48 addressing impaired mobility, five addressing nutrition, three addressing impaired skin condition and three addressing turning and positioning.[35] The data confirmed that pressure-reducing devices appear to have an advantage over standard beds, but little difference has been shown between devices. No trial of measures for impaired skin met criteria for study design and only one trial of turning and positioning suggested a reduction in pressure ulcer incidence.

Nutrition in preventing pressure ulcers

Nutritional status has been thought to influence the incidence, progression and severity of pressure sores.[36] Experimental studies in animal models suggest a biologically plausible relationship between undernutrition and development of pressure ulcers. When pressure was applied for 4 h to the skin of both well-nourished and malnourished animals, pressure ulcers occurred equally in both groups. However, the degree of ischaemic skin destruction was more severe in the malnourished animals. Epithelialization of the pressure lesions occurred in normal animals at 3 days post-injury, whereas necrosis of the epidermis was still present in the malnourished animals.[37] This data suggest that although pressure damage may occur independently of nutritional status, malnourished animals may have impaired healing after a pressure injury.

The primary link between pressure ulcers and nutritional status derives from epidemiological observational studies. For example, at hospital admission, patients who are defined as undernourished are twice as likely to develop pressure ulcers as non-undernourished patients.[38] In a long-term care setting, 59% of residents were diagnosed as undernourished on admission. Among these residents, 7.3% were classified as severely undernourished. Pressure ulcers occurred in 65% of these severely undernourished residents. No pressure ulcer developed in the mild to moderately undernourished or well-nourished groups.[39]

Recent advances in the understanding of nutritional deficiencies have given rise to a re-examination of these observational data. The association of undernutrition with pressure ulcers is problematic, because there is no accepted gold standard for the diagnosis of undernutrition. Body weight loss and reductions in acute-phase hepatic proteins are often used as criteria for the diagnosis of undernutrition. However, the markers used for the diagnosis of nutritional status may reflect underlying disease rather than undernutrition in older ill persons. Cachexia and wasting diseases also produce weight loss and decreases in acute-phase reactants such as albumin and prealbumin.[40]

This critical distinction between undernutrition and the effect of wasting diseases is important because undernutrition due to starvation can be reversed by provision of adequate nutrients. Cachexia and wasting diseases are remarkably resistant to hypercaloric feeding.[41] This overlap between undernutrition and cachexia may account for the disappointing results of nutritional interventions in the prevention of pressure ulcers. A systematic review of nutritional intervention for prevention of pressure ulcers found only one of four trials suggesting that nutritional supplements may reduce the incidence of pressure ulcers in critically ill older persons.[42] In the single positive trial, two drinks of a mixed nutritional supplement produced a modest effect size at 15 days. The cumulative incidence of pressure ulcers was 40% in the nutritional supplemented group compared with 48% in the control group.[43]

Pressure ulcer incidence as a quality of care indicator

If pressure ulcers can be prevented, then the presence of a pressure ulcers may be an indicator of quality of care.[44,45] However, if adequately applied prevention interventions are not effective, the link between pressure ulcer incidence and quality of care is severed.[46]

In surveys of prevention practices among hospitalized Medicare beneficiaries, there was no link between documentation of a quality indicator and the incidence of pressure ulcers. In a multicentre retrospective cohort study of 2425 patients aged 65 years and older discharged from acute care hospitals, six processes of care for prevention of pressure ulcers were evaluated, including use of daily skin assessment, use of a pressure-reducing device, documentation of being at risk, repositioning for a minimum of 2 h, nutritional consultation initiated for patients with nutritional risk factors and staging of pressure ulcer. In

fact, older adults who had documentation of being at risk and/or who received a pressure-reducing device and/or were turned every 2 h had a higher incidence of pressure ulcer development.[47]

Compliance with quality indicators in 16 nursing facilities in California was assessed after dividing the homes into those with the highest or the lowest quartile incidence of pressure ulcers. The homes in the lowest quartile had a 2.7–5.5% incidence of pressure ulcers whereas the high quartile nursing facilities had a 16.6–29.8% incidence of pressure ulcers. Sixteen process of care quality indicators were assessed, including 10 specific to pressure ulcers. No differences in the pressure ulcer quality indicators derived from the Minimum Data Set was observed between nursing facilities with low and high pressure ulcer incidence. Moreover, there was no difference in direct clinical observation of processes of care between nursing facilities with low and high pressure ulcer incidence.[48]

In 20 facilities with Medicare-certified beds, 12 quality indicators were derived from expert opinion and data available in the Minimum Data Set. An intensive intervention included education, direct facility assistance and multiple site visits by study personnel. The result of the intervention was positive, that is, the facilities showed improvement in eight out of 12 quality indicators. The trial suggests that nursing facility can improve documentation of care in relationship to pressure ulcers. However, there was no improvement in four of the 12 quality indicators. Most importantly, there was no improvement in the incidence of pressure ulcers despite the relatively intense intervention. No difference was observed in the proportion of low-risk residents who developed a pressure ulcer during their stay or in the proportion of high-risk residents who developed a pressure ulcer during their stay.[49]

In a study of 35 self-selected nursing homes, an educational intervention improved compliance with pressure ulcer risk assessment (from 87 to 99%) and weekly wound assessment (from 45 to 67%). There was little change in the incidence of Stage II pressure ulcers (from 2.6 to 2.0 per 100 occupied beds per month) but the incidence of Stage II–iv pressure ulcers declined from 3.2 2.3 per 100 occupied beds per month from the first 3 months to the last 3 months over an 11 month period. The median per facility incidence of Stage III and IV pressure ulcers declined from 0.31 pressure ulcers per 100 occupied beds per month in the first 3 months to 0 per 100 beds per month in the last 3 months of observation. Nevertheless, of the 35 study facilities, an incident Stage III or IV pressure ulcer developed in 28 of the facilities.[50]

These data suggest that the development of pressure ulcers may not be as tightly linked to quality of care processes as has been suggested. Systematic efforts at education, heightened awareness of pressure ulcer prevention and specific interventions by interdisciplinary wound teams suggest that a high incidence of pressure ulcers can be reduced. Over time, reductions in incidence of pressure ulcers of 25–30% have been reported.[51,52] The reduction may be transient, unstable over time, vary with changes in personnel or occur due to random variation.[53] However, no trial has reported an elimination of pressure ulcers over time and a 'floor effect' for pressure ulcer incidence has been noted, despite aggressive measures for prevention.[54] These data confirm a growing body of evidence that severs the hypothesized link between pressure ulcer incidence and quality of care indicators. The data suggest that pressure ulcers can be, but not always are, measures of quality of care.

Treatment of pressure ulcers

Pressure ulcers are chronic wounds. Acute wounds proceed to healing through a well-researched sequential progression towards healing. Pressure ulcers, like other chronic wounds (diabetic ulcers, venous stasis ulcers and arterial ulcers), fail to proceed through an orderly and timely process to produce anatomical or functional integrity.

Normally, fibroblasts and epithelial cells grow rapidly in skin tissue cultures, covering 80% of *in vitro* surfaces within the first 3 days. In contrast, biopsy specimens from pressure ulcers usually do not grow until much later, covering only 70% of surfaces by 14 days.[55] The result is slow healing. About 75% of Stage II pressure ulcers healed in 8 weeks, but only 17% of Stage III or IV pressure ulcers healed in that time.[56] About 23% of Stage II pressure ulcers remained unhealed at 1 year and 48% of Stage IV pressure ulcers were unhealed at 1 year. At 2 years, 8% of Stage II pressure ulcers, 29% of Stage III pressure ulcers and 38% of Stage IV pressure ulcers remained unhealed.[57] The considerable length of time to healing increases the morbidity and cost of treating pressure ulcers and is often frustrating to the patient and caregivers.

Relieving pressure, friction and shear

Although there is clear evidence that pressure reduction leads to a decrease in pressure ulcer incidence, few trials have examined the effect of pressure reduction on the healing of pressure ulcers. Two short-duration trials of air-fluidized therapy have been associated with improved rates of closure of pressure ulcers in hospital settings, but not in longer duration home trials. A low-air-loss bed is superior to a convoluted foam mattress. Other trials directly comparing different devices for improved healing have not shown a difference among devices.[58] Given the data on pressure ulcer prevention, it is reasonable to conclude that pressure-reducing devices may improve healing of pressure ulcers.

Topical dressings and local wound care

Local wound treatment is directed at providing an optimum wound environment and improving host factors. The most commonly used dressing for pressure ulcers at hospital discharge in the USA is dry gauze.[59] The use of dry gauze persists despite clear data suggesting that it results in delayed healing. Compared with wet-to-dry gauze dressings, moist dressings are clearly superior. Moist wound healing allows experimentally induced wounds to resurface up to 40% faster than air-exposed wounds.[60]

The concept of a moist wound environment led to the development of occlusive dressings. The term 'occlusive' describes the inability of a dressing to transmit moisture vapour from the wound to the external atmosphere. The degree to which dressings dry the wound can be measured by the moisture vapour transmission rate (MVTR). An MVTR of less than 35 g of water vapour per square meter per hour is required to maintain a moist wound environment. Woven gauze has an MVTR of 68 g m^{-2} h^{-1} and impregnated gauze has a MVTR of 57 g m^{-2} h^{-1} In comparison, hydrocolloid dressings have an MVTR of 8 g m^{-2} h^{-1}.[61]

Occlusive dressings can be divided into broad categories of polymer films, polymer foams, hydrogels, hydrocolloids, alginates and biomembranes. Each has several advantages and disadvantages. The available agents differ in their properties of permeability to water vapour and wound protection. Understanding these differences is the key to planning for wound management in a particular patient.[62]

Comparative qualities among available agents are shown in Table 126.3. Most of the occlusive dressings offer pain relief. Only absorbing granules fail to reduce pain. Polymer films are impermeable to liquid but permeable to gas and moisture vapour. Because of low permeability to water vapour, these dressings are not dehydrating to the wound. Non-permeable polymers such as polyvinylidine and polyethylene can be macerating to normal skin. Polymer films are not absorptive and may leak, particularly when the wound is highly exudative. Most films have an adhesive backing that may remove epithelial cells when the dressing is changed. Polymer films do not eliminate deadspace and do not absorb exudate.

Hydrocolloid dressings are complex layered dressings. They are impermeable to moisture vapour and gases and are highly adherent to the skin. Their adhesiveness to surrounding skin is higher than that of some surgical tapes, but they are non-adherent to wound tissue and do not interfere with epithelialization of the wound. The adhesive barrier of a hydrocolloid dressing can be overcome in highly exudative wounds. Excessive exudate may be overcome with an absorptive dressing such as calcium alginate.

Hydrogels are three-layer hydrophilic polymers that are insoluble in water but absorb aqueous solutions. They are poor bacterial barriers and are non-adherent to the wound. Because of their high specific heat, these dressings are cooling to the skin, aiding in pain control and reducing inflammation. Most of these dressings require a secondary dressing to secure them to the wound.

Alginates are complex polysaccharide dressings that are highly absorbent in exudative wounds. This high absorbency is particularly suited to exudative wounds. Alginates are non-adherent to the wound, but if the wound is allowed to dry, damage to the epithelial tissue may occur with removal. Alginates can be used under a number of dressings to control exudate, including hydrocolloids.

Hydrocolloid dressings and biomembranes do not allow bacteria on the surface of the dressing to penetrate to the wound. Biomembranes are tissue-derived dressings designed to cover the wound and provide potential wound healing factors. The biomembranes are very expensive and not readily available.

Table 126.3 Comparison of occlusive wound dressings.

Item	Moist saline gauze	Polymer films	Polymer foams	Hydrogels	Hydrocolloids	Alginates, granules	Biomembranes
Pain relief	+	+	+	+	+	±	+
Maceration of surrounding skin	±	±	−	−	−	−	−
O_2 permeable	+	+	+	+	−	+	+
H_2O permeable	+	+	+	+	−	+	+
Absorbent	+	−	+	+	±	+	−
Damage to epithelial cells	±	+	−	−	−	−	−
Transparent	−	+	−	−	−	−	−
Resistant to bacteria	−	−	−	−	+	−	+
Ease of application	+	−	+	+	+	+	−

Adapted from Helfman T, Ovington L and Falanga V. Occlusive dressings and wound healing. *Clin Dermatol* 1994;**12**:121–7 and Witkowski JA and Parish LC. Cutaneous ulcer therapy. *Int. J Dermatol* 1986;**25**:420–6.

The dressings differ in the ease of application. This difference is important in pressure ulcers in unusual locations or when considering home care. Dressings should be left in place until wound fluid is leaking from the sides, a period of days to 1 week.

A meta-analysis of five clinical trials comparing a hydrocolloid dressing with a dry dressing demonstrated that treatment with a hydrocolloid dressing resulted in a statistically significant improvement in the rate of pressure ulcer healing (odds ratio 2.6).[63] Hydrocolloid dressings demonstrated higher healing rates compared with moist gauze in four of the five trials. Topical application of collagen showed no significant differences in healing compared with a hydrocolloid. Collagen was more expensive and offered no major benefits to patients otherwise eligible for hydrocolloid treatment.[64]

A systematic review of published trials on topical wound dressings for pressure ulcers up to 2003 found only 21 published randomized controlled trials.[65] Hydrocolloid wound dressings were superior to saline dressings in six trials, whereas comparisons in five trials using other treatment modalities (dextranomer beads, paraffin gauze, polyurethane dressing, amorphous hydrogel) showed no differences compared with saline gauze. In nine trials comparing hydrocolloid dressings with various other advanced dressings, no difference was observed between the intervention and comparison groups. A trial comparing two different polyurethane dressings showed no difference.

A number of growth factors have been demonstrated to mediate the healing process, including transforming growth factor alpha and beta, epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, interleukin 1 and 2 and tumour necrosis factor alpha.[66] Accelerating healing in chronic wounds by using these acute wound factors is attractive. In pressure ulcers, platelet-derived growth factor failed to produce complete healing,[67] although improved time to closure of wounds has been shown with PDGF-BB and basic fibroblast growth factor.[68,69] Topical nerve growth factor is superior to vehicle-only treated patients for pressure ulcers of the foot. Complete healing of a pressure ulcer occurred in eight subjects in the active treatment group but in only one subject in the vehicle control group. Improvement was greater (based on wound size) in the active treatment group than in the vehicle-only group.[70] The development of wound healing factors is still in its infancy but shows great promise.[71]

Vacuum-assisted closure has been used in both acute and chronic wounds. Only two randomized controlled trials on pressure ulcers have been reported. A total of 22 patients with 35 pressure ulcers were randomized to the vacuum-assisted closure device or a system of wound gel products for 6 weeks. Two patients in the vacuum-assisted closure group and two patients in the wound gel group showed complete healing. There was no difference in reduction in ulcer volume between groups.[72] Vacuum-assisted closure was compared with gauze moistened with Ringer's solution in a small trial of pressure ulcer treatment. The time to reach 50% of the initial wound volume was 27 days in the vacuum-assisted group and 28 days in the moist gauze-treated group.[73] Overall, seven randomized controlled trials have compared vacuum-assisted closure in various types of chronic wounds. Four trials compared gauze soaked in either normal saline or Ringer's solution. A further three trials compared vacuum therapy with hydrocolloid gel plus gauze, a papain–urea topical treatment and cadexomer iodine or hydrocolloid, hydrogels, alginate and foam. The results did not show that vacuum-assisted closure significantly increases the healing rate of chronic wounds.[74]

A review of various pressure ulcer treatments was performed over a 6 month period across several healthcare settings. The analysis focused on complete healing as the primary outcome measure. Not surprisingly, those patients with larger ulcer size and a higher wound severity score healed less often than others. Surprisingly, the use of a pressure-relieving device, documentation of a turning schedule or the use of nutritional supplements was associated with less likelihood of healing. Furthermore, the application of topical antiseptics, use of enzymatic debridement and administration of antibiotics all significantly reduced the chances of healing. Pressure ulcers that healed in this study used more 'modern' dressings (such as a hydrocolloid dressing), used more exudate management dressings, had fewer wound debridements (especially mechanical debridement) and had fewer changes in dressing type over the course of healing. Patients residing at a nursing home had more enzymatic debridement and more were given antibiotics, despite having fewer documented infections. Despite these differences in management, the rate of healing in the nursing home population was not different from that in the community-dwelling patients. The multivariate analysis of factors associated with healing demonstrated that patients having Medicaid coverage, cardiovascular disease, frequent changes of dressing type, application of a topical antiseptic, received antibiotics or who used a pressure-relief device had a reduced likelihood of healing. Only the use of an exudate absorptive dressing was associated with an increased likelihood of healing.[75] These data are likely confounded by more severe wounds receiving more complex interventions, but no clear benefit was demonstrated for any specific modality.[76]

Nutritional interventions for healing

Nutritional interventions for the healing of pressure ulcers rests on the theory that undernourished patients do not ingest sufficient energy, proteins, vitamins or minerals to provide for adequate wound healing. Based on this

assumption, a number of nutritional interventions have been trialled in the healing of pressure ulcers. The results have been uniformly disappointing.[77]

An optimum dietary protein intake in patients with pressure ulcers is unknown, but may be higher than current adult recommendations of 0.8 g kg^{-1} per day. Half of the chronically ill elderly persons are unable to maintain nitrogen balance at this level.[78] Increasing protein intake beyond 1.5 g kg^{-1} per day may not increase protein synthesis and may cause dehydration.[79] A reasonable protein requirement is therefore between 1.2 and 1.5 g kg^{-1} per day. Specific amino acids such as arginine and branched-chain amino acids have not demonstrated an effect on pressure ulcer healing.[77]

The deficiency of several vitamins has significant effects on wound healing. However, supplementation of vitamins to accelerate wound healing is controversial. High doses of vitamin C have not been shown to accelerate wound healing.[80] In a 12 week study of 88 patients who received either 10 or 500 mg of ascorbic acid twice daily, the healing rates and the healing velocity of their pressure ulcers were not different in the higher dosed group.[81] Zinc supplementation has not been shown to accelerate healing except in zinc-deficient patients.[82] High serum zinc levels interfere with healing and supplementation above 150 mg per day may interfere with copper metabolism.[36]

The use of enteral feeding has been disappointing. In a study of enteral tube feedings in long-term care, 49 patients were followed for 3 months.[83] Patients received 1.6 times basal energy expenditure daily, 1.4 g of protein per kilogram per day and 85% or more of their total recommended daily allowance. At the end of 3 months, there was no difference in number or healing of pressure ulcers. In a study of survival among residents in long-term care with severe cognitive impairment, 135 residents were followed for 24 months.[84] The reasons for the placement of a feeding tube included the presence of a pressure ulcer. Having a feeding tube was not associated with increased survival; in fact, the risk was slightly increased. These data suggests that the effectiveness of enteral feeding in treating pressure ulcers is not established.

Wound debridement

Necrotic debris increases the possibility of bacterial infection and delays wound healing in animal models.[85] This delay in healing results from slow removal of debris required by phagocytosis. Although widely recommended, it remains unclear whether wound debridement is a beneficial process that results in a greater frequency of complete wound healing.[86] There are no studies that compared debridement with no debridement as the control in wound healing. The use of debridement can result in a shorter time to a clean wound bed in anticipation of surgical therapy.

Options for debridement include sharp surgical debridement, mechanical debridement with dry gauze dressings, autolytic debridement with occlusive dressings or application of exogenous enzymes. Surgical sharp debridement produces the most rapid removal of necrotic debris and is indicated in the presence of infection. Surgical or mechanical debridement can damage healthy tissue or fail to clean the wound completely. Mechanical debridement can be easily accomplished by letting saline gauze dry before removal, but may produce pain with removal. Re-moistening of gauze dressings in an attempt to reduce pain can defeat the debridement effect.

Thin portions of eschar can be removed by occlusion under a semi-permeable dressing. Enzymatic debridement can dissolve necrotic debris but possible harm to healthy tissue is debated. Penetration of enzymatic agents is limited in eschar and requires either softening by autolysis or cross-hatching by sharp incision prior to application. Both autolytic and enzymatic debridement require periods of several days to several weeks to achieve results.

The only enzyme product available in the USA for topical debridement is collagenase. Formerly used papain–urea and a papain–urea–chlorophyll combination is unavailable. A trial in 21 patients with pressure ulcers found a greater reduction in necrotic tissue using papain–urea (95.4%) compared with collagenase (35.8%) at 4 weeks, but the rate of complete healing was not different between groups.[87]

A total of five trials have not shown that enzymatic agents increased the rate of complete healing in chronic wounds compared with control treatment.[86] One trial showed an increase in wound size with both collagenase and the control treatment, but the increase was significantly less in the enzyme-treated group. Only one trial out of four that compared a hydrogel with a control treatment found a statistically significant difference between treatments. The single favourable trial suggested a small benefit from treatment with a hydrogel compared with a hydrocolloid dressing. In a single trial comparing different hydrogels, no statistically significant difference was seen between the two hydrogels.

Trials of other debridement agents have shown mixed results. Three trials of dextranomer polysaccharide found a statistically significant difference compared with control, and two trials found the control treatment to be more effective. A hydrogel significantly reduced the necrotic wound area compared with dextranomer polysaccharide paste in one trial, but not in another. Dextranomer polysaccharide was not better than an enzymatic agent in two trials.

A number of heavy metal-impregnated dressings or solutions have been evaluated for chronic wounds, based on the hypothesis that an antimicrobial effect would enhance wound healing. Topical silver and silver-impregnated dressings have been evaluated in three trials of mixed-type wounds suspected of being infected.

Only one trial included pressure ulcers as a wound type. In that trial, there was no difference in complete healing or absolute or relative wound size, but a small effect was calculated for healing rate per day.[88,89]

Conclusion

The accumulating data for the prevention and management of pressure ulcers permit an outline of clinical strategies. Risk assessment remains problematic because of poor predictive validity and an apparent floor effect in preventing all pressure ulcers, but can highlight patient-specific risk factors for development of a pressure ulcer. Pressure-reducing devices are clearly superior to a standard hospital mattress in preventing pressure ulcers. However, it is difficult to distinguish superiority among various devices. The impact of nutrition on the prevention of pressure ulcers remains controversial. Limited data suggest than nutritional supplementation may have an effect on reducing incidence. Nutritional status should be evaluated in all clinical settings as a process of good care.

Limited evidence and clinical intuition support pressure-reducing devices in improving the healing rate of pressure ulcers. The amount of dietary protein intake seems to be linked to improved rates of healing, but the results of enteral feeding to achieve this result are disappointing. Other nutritional interventions, including specific amino acids and vitamin or mineral supplements, have not shown an effect on healing rate.

Local wound treatment should aim at maintaining a moist wound environment. Options include hydrocolloid dressings and other occlusive moist dressings. The choice of a particular dressing depends on wound characteristics such as the amount of exudate, deadspace and wound location. Debridement by any of several methods may improve the time to a clean wound bed, but the effect of debridement on time to healing remains to be demonstrated. The use of topical growth factors in improving healing rates is in its infancy but has not been remarkably effective thus far.

Key points

- Pressure ulcers are related to pathological changes in the blood supply to the tissues.
- Pressure relief prevents and helps with healing of pressure ulcers.
- Hydrocolloid wound dressings are superior to saline dressings.
- There is weak evidence to support supplemental nutrition interventions to improve pressure ulcer healing rates.

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CHAPTER 127

Perioperative and postoperative medical assessment

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Introduction

Since 1850, life expectancy has increased linearly.[1] With increase in life expectancy comes an increase in medical needs for adults in late life, including surgical procedures. In 2006, inpatient procedures were performed on 4358 per 10 000 patients over the age of 65 years. Surgeons have seen an increase in the rates of certain procedure types over the last decade in this age group. As an example, the rate of total knee replacements increased from 60 per 10 000 population in 2000 to 88 per 10 000 population in 2006.[2] It is estimated that more than half of people currently over the age of 65 years will undergo at least one surgical procedure.[3] As the population grows and ages, the need for specialized surgical care of the elderly will grow. The role of the consulting geriatric specialist is to assist the surgeon in maximizing preoperative function, minimizing the effect of comorbid diseases and preventing or managing postoperative complications.[4]

The approach to perioperative management of the geriatric patient begins with an understanding of age-related changes in physiology and how these changes affect stress responses. Preoperatively, the consultant should identify patients at risk for adverse outcomes, with the intent of maximizing function and minimizing risk. Although often not modifiable, intraoperative factors, such as type of procedure, type of anaesthesia and occurrence of complications, may affect the outcome in elderly patients. Prior to surgery, ways to minimize procedure length and complications should be considered by the operative team, which includes the surgeon, anaesthesiologist and consulting geriatrician. Anticipation of potential postoperative complications leads to early identification and management of adverse outcomes. The most common postoperative complications are cardiac, pulmonary and neurological in origin. Strategies to minimize the risk to these organ systems have been studied and some guidelines exist to assist with management. Prevention and treatment of infection and venous thromboembolism begin in the preoperative period and can also greatly improve outcome. Several other problems can occur postoperatively and the consulting geriatric specialist can help ameliorate those problems with simple multidisciplinary interventions.

The aim of this chapter is to guide the geriatric specialist in perioperative risk assessment and reduction with the goal of lowering complications and improving outcomes. It focuses on evaluation and management of the geriatric patient undergoing non-cardiac surgery. For a discussion on cardiac surgery in the elderly, see Chapter 42.

Outcomes of surgery in the elderly

Survival curves from the UK show an increase in life expectancy with a continual rightward shift since 1850[1] (see Figure 127.1).[5] This argues against the theory of a biologically determined limit to life. However, as mortality shifts, epidemiologists have observed a decompression of morbidity. This means that humans are living longer with more years lived in poor health.

Studies of elderly surgical patients consistently showed poorer outcomes in people over the age of 65 years versus their younger counterparts.[4,6,7] However, when adjusted for comorbid conditions, type and length of procedure or preoperative physical state [as assessed using American Society of Anesthesiologists' (ASA) classification or similar grading tool], the risk of adverse outcomes attributed to age alone is significantly diminished.[4,6] A description of the ASA classification system can be found on the ASA website.[8] A retrospective study carried out at the end of the twentieth century showed a postoperative complication rate of 25% in patients over the age of 80 years, consistent with other studies. Although this number may be troubling, 74% of the cohort did well, with no complications, and the mortality rate was only 4.6%,

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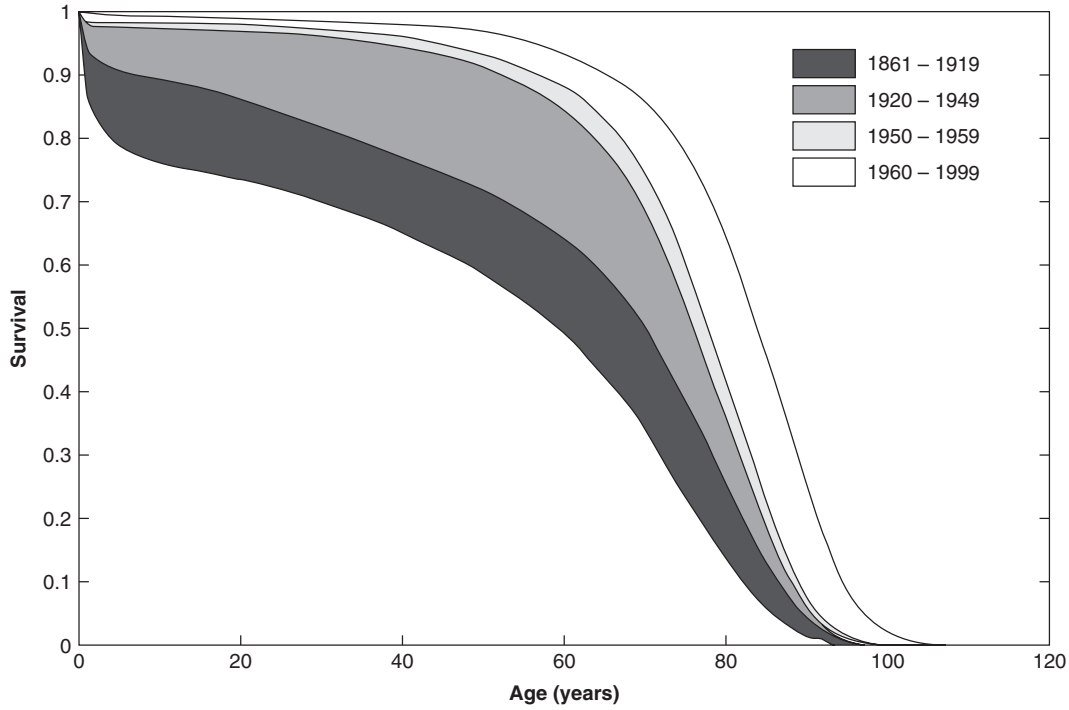


Figure 127.1 Survival curves in Sweden over the last 140 years. Initial survival improvement trends showed a rectangularization of the survival curve, followed by parallel rightward shifts. Reprinted from Smetana,[4] Copyright 2003, with permission from Elsevier.

down from 20% in the 1960s.[9] For this reason, surgery should not be denied based solely on age. Instead, a comprehensive preoperative assessment that determines risk and maximizes function should drive decisions to proceed with surgery, even in the oldest old.

Ageing physiology

Normal physiological changes occur with ageing. These changes should not be viewed as pathological conditions since under normal circumstances the body is able to compensate. During periods of stress, such as surgery or trauma, the ageing body is less able to counter the insult and complications may ensue.[3] An understanding of normal age-related physiological changes helps the geriatric specialist to maximize functional reserve and provide adequate physiological support perioperatively. Note that although these organ system changes occur consistently with ageing, they do not occur at the same rate in each individual, such that there is often a discrepancy between the chronological age and biological age. Therefore, perioperative management must be individualized.

Age-related changes in the cardiovascular system

As humans age, the physiology of the cardiovascular system undergoes numerous changes that affect vascular compliance, blood pressure and myocardial contractility. Blood vessels lose compliance due to calcification, tunica media thickening and elastic fracturing. As a result, systolic blood pressure is often elevated. However, a blunted response to baroreceptor activity predisposes the elderly to orthostatic hypotension. Changes in the peripheral vascular system cause an increase in afterload leading to myocardial hypertrophy. Cellular hypertrophy, along with calcification and fibrosis, brings about diastolic dysfunction and damage to pacemaker cells. As the ventricles stiffen, left ventricular end diastolic volume and cardiac output diminish. Increased preload with atrial enlargement compensates for the reduced cardiac output; therefore, losing atrial contraction as a result of atrial fibrillation can lead to cardiac decompensation.[3,10] Cardiovascular response to stress is also altered with age. Older people have blunted beta-adrenergic sensitivity and also reduced basal vagal tone with an inability to lower vagal tone further, leading to an inappropriate heart rate response to stress.[3]

Age-related changes in the pulmonary system

As in the vascular system, changes in the pulmonary system associated with ageing are largely due to loss in elasticity. This loss of elastic recoil of the lungs decreases oxygen transfer and air trapping. Muscle atrophy and joint damage impair chest wall movement, further reducing ventilation

and oxygenation. Vital capacity and FEV1 are decreased, in addition to ciliary function. An increase in residual volume leads to an increase in dead space during normal breathing. These age-related changes increase risk of atelectasis, aspiration and pneumonia postoperatively.[3,10]

Age-related changes in the renal system

Reduced cardiac output, reduced renal mass and glomerulosclerosis cause a decrease in renal plasma flow and glomerular filtration rate (GFR) with age. Renal clearance is slowed, affecting drug elimination and acid excretion. Patients with renal insufficiency are at higher risk of volume overload, electrolyte imbalances and drug accumulation. However, ageing kidneys also have a reduced capacity to concentrate urine, even when fluid intake is inadequate, predisposing the person to dehydration. Creatinine clearance must be calculated prior to surgery for appropriate administration of fluids, anaesthesia and pain medication.[3,10] Laboratory estimates of GFR may not be accurate in elderly populations.

Age-related changes in the neurological system

The major change associated with ageing of the nervous system is loss of neuronal substance, with a decrease in brain weight. Peripheral neurons also decrease in number. This age-related loss of neuronal mass may explain the increased sensitivity to opioids and anaesthetics seen in elderly patients.

Emergency surgery

Emergency surgery has long been associated with increased mortality rates over elective surgery.[11,12] The questions remain of whether age further increases mortality, when emergency surgery should be denied or delayed for resuscitation and if any interventions instituted prior to surgery could ameliorate the risk of mortality in the elderly.

Several observational studies have been carried out to identify the risk factors for mortality in patients undergoing emergency surgery.[11–13] Most were orthopaedic, trauma or general surgery. Mortality rates were consistently higher for elderly patients and those with high ASA classes (three or higher). The leading causes of death were malignancy and septic or cardiac complications. Orthopaedic patients tended to have a more favourable outcome than general surgery patients because limb procedures are less likely to produce cardiopulmonary, metabolic or gastrointestinal (i.e. ileus) complications. Additionally, they were often labelled as 'urgent', meaning the operations took place within 24 h as opposed to immediate (within 1–2 h), allowing some time for stabilization and preparation.[11,12] Current guidelines recommend avoiding night-time operations; however, recent studies suggest that this may be unfounded as no association was found between late-night surgery and increased mortality.[11,12]

A study restricted to elderly patients (50% over the age of 80 years) undergoing emergency abdominal surgery found that mortality rates were affected by preoperative risk (increase in comorbid conditions, high ASA class), delay in diagnosis and surgical treatment and conditions only allowing palliative surgery or non-therapeutic laparotomy. After adjusting for these conditions, age alone did not affect mortality, morbidity or length of stay.[13] Emergency surgery should not be denied to patients strictly based on age.

The above studies suggest that perioperative interventions (particularly during and immediately after surgery), such as appropriate antimicrobial prophylaxis, limiting surgery length and a consideration to delay surgery for stabilization of patients with ASA class 4 or 5, *may* improve outcomes. Prospective studies assessing these interventions are needed.

Preoperative medical assessment of the geriatric patient

Multiple studies have been done to assess the perioperative risks of elderly patients. Several are reviewed in this chapter, with emphasis on current guidelines and recommendations. It is worth noting that although identification of factors associated with postoperative complications is helpful for risk stratification, they are often not modifiable. Additionally, although as a group patients at high surgical risk have far more complications than those at low risk, risk indices cannot predict which *individual* will have a poor outcome. Many patients at high risk have uneventful surgical courses. Continued research to delineate cost-effective interventions most likely to reduce adverse events that can be widely applied to the elderly surgical patient is needed.

Review of data reveals that postoperative complications, including cardiopulmonary events, neurological events or death, are more likely to occur in the setting of poor premorbid function or emergency surgery.[10] Preoperative factors most likely to increase risk of morbidity and mortality include the following:[9,10,14,15]

1 severe systemic disease (ASA Class III–V)
2 acute or chronic renal failure
3 history of chronic obstructive pulmonary disease (COPD) or congestive heart failure
4 recent (within 6 months) myocardial infarction (MI)
5 low albumin level ($<3.5\ g\ dl^{-1}$)
6 anaemia (haemoglobin $<8\ g\ dl^{-1}$)
7 poor functional status (bedridden, assistance with ADL or inability to perform 2 min on a supine bicycle exercise test)
8 impaired sensorium or cognition.

Based on the above factors, preoperative medical evaluation begins with a thorough history emphasizing comorbid diseases and functional status. The physical examination should focus on signs of active cardiopulmonary disease (such as jugular venous distension, rales, an S3 gallop, oedema and wheezing) and evaluation of cognitive status. Basic laboratory evaluation and radiological procedures should be obtained based on history and examination findings.[10,16] For most patients, the initial preoperative workup includes a complete blood count, electrolyte levels, renal function and electrocardiogram (ECG). It should be noted that although several sensitive risk indices exist to predict potential postoperative complications, the risk criteria are not specific. Many patients with multiple risk factors will have uncomplicated operative courses.[14]

Cardiac risk assessment

The most widely published topic in preoperative surgical evaluation is cardiac risk assessment. A PubMed search for 'perioperative cardiac risk assessment' brings up over 1000 articles and nearly 300 reviews. When limited to articles addressing cardiac risk in patients over 65 years of age, 500 articles and 30 reviews are listed. Current guidelines exist to aid the clinician in cardiac risk evaluation, including the 2007 American College of Cardiology/American Heart Association (ACC/AHA) Preoperative Cardiac Risk Assessment.[16] The ACC/AHA guideline utilizes the Revised Cardiac Risk Index (derived from Goldman *et al*.[17] and Lee *et al*.[18]) for stratification and is the most widely used.

The purpose of a cardiac evaluation prior to surgery is threefold:

1 To identify patients with active unstable cardiac disease, for whom surgery ought to be delayed or cancelled for medical management.

2 To identify patients at high risk for postoperative cardiac complications in order to devise interventions to modify and minimize the risk.

3 To identify patients with risk factors for coronary artery disease who should undergo preoperative cardiac testing and receive perioperative beta-blockers.

Table 127.1 lists unstable cardiac conditions that require stabilization prior to non-emergent surgery and strategies for management of surgical patients requiring revascularization.[16]

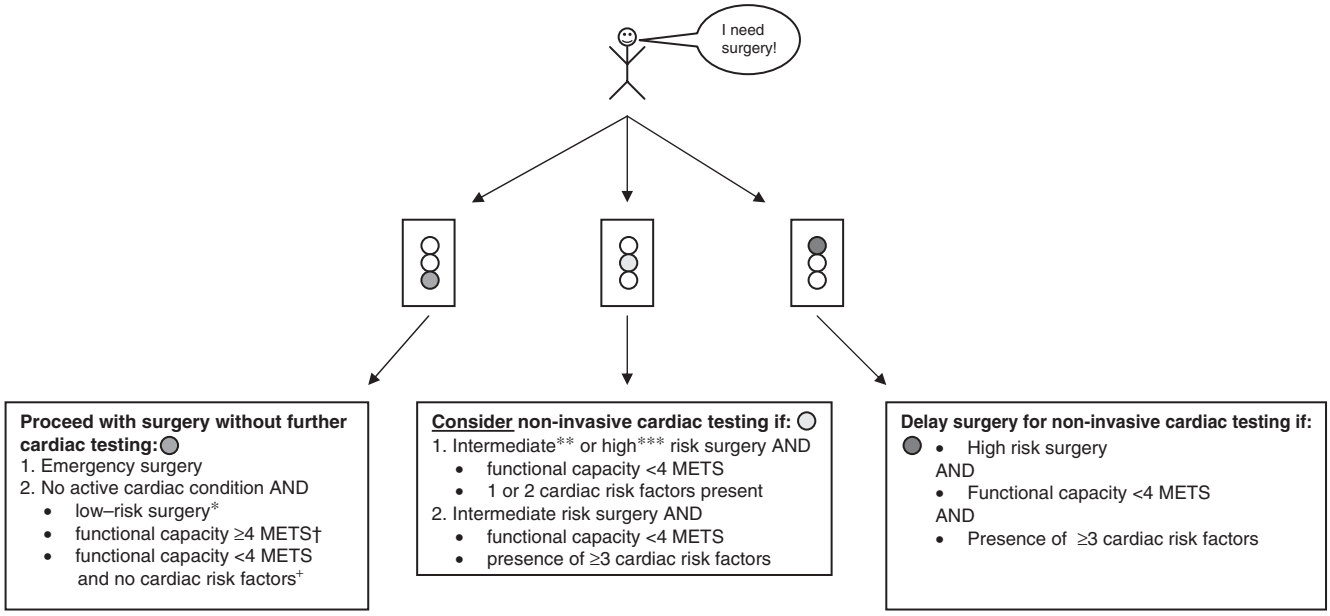
Goldman *et al*.[17] devised and validated the first Cardiac Risk Index based on 13 parameters in six categories (including history, physical, electrocardiogram, general health status and type of operation). This index was revised in 1999 and included in the ACC/AHA guidelines for evaluation of cardiac risk. The Revised Cardiac Risk Index is based on six clinical parameters that carry postoperative prognostic significance:[18] high-risk surgery, history of ischaemic heart disease, history of or active heart failure, history of cerebrovascular disease, diabetes mellitus requiring insulin therapy and renal insufficiency (serum creatinine $>2.0\,mg\,dl^{-1}$). Preoperative functional status can also be used to identify risk for cardiac complications.[10,16,18]

Figure 127.2 outlines an approach to evaluating and managing cardiac risk based on the Revised Goldman Cardiac Risk Index and the 2007 ACC/AHA Guidelines.[16,18]

Once it has been determined that non-invasive cardiac stress testing is needed, the consultant must decide which test to perform. The test of choice for ambulatory patients is exercise ECG testing.[16] Exercise testing provides information on cardiac ischaemia and functional status, both predictive of surgical outcomes. Its safety is established[16]

Table 127.1 Management in non-emergent surgery for unstable cardiac conditions.

Defer surgery for management of:	Myocardial infarction within 30 days
	Unstable or severe angina
	Decompensated heart failure
	Severe aortic stenosis (pressure gradient >40 mmHg, valve area <1 cm^2 or symptoms)
	Symptomatic mitral stenosis
	Significant unstable arrhythmias
Refer for PTCA or CABG if:	Stable angina and significant left main disease
	Stable angina and triple-vessel disease
	Stable angina and two-vessel disease *with* proximal LAD lesion and EF <50% or ischaemia on testing
	Unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI)
	ST-segment elevation myocardial infarction (STEMI)
Defer elective surgery post-PTCA for:	<14 days from balloon angioplasty
	<30 days from bare metal stent placement
	<12 months from drug-eluding stent placement



* Low risk surgery = endoscopic procedures, superficial procedures and cataract, breast and ambulatory surgeries carry <1% risk of sustaining a perioperative cardiac event

** Intermediate risk surgery = all surgeries that do not fall into low or high risk categories carry 1–5% risk of sustaining a perioperative cardiac event

*** High risk surgery = vascular surgery (aortic or other major vascular procedure and peripheral vascular surgery) carry >5% risk of sustaining a perioperative cardiac event)

† 4 METS of activity = light housework or ability to climb a flight of stairs or walk up a hill

+ Cardiac risk factors are defined by the Revised Goldman Cardiac Risk Index

Figure 127.2 Decision tree for evaluation of cardiac risk prior to surgery. See plate section for a colour version of this image.

and studies on elderly patients have shown that a simple supine bicycle exercise test can predict exercise capacity and perioperative cardiac complications better than more expensive and complicated cardiac testing.[14]

If abnormalities exist on baseline resting ECG (e.g. left bundle-branch block, LV hypertrophy with 'strain' pattern or digitalis effect) or if patients are unable to exercise, pharmacological stress cardiac imaging is recommended.[16]

If non-invasive cardiac testing is positive, the patient ought to be referred for percutaneous transluminal coronary angioplasty (PTCA). Following PTCA, the patient is at high risk for restenosis and cardiac decompensation under stressful conditions. Additionally, patients who undergo revascularization require dual antiplatelet therapy to reduce the risk of restenosis. For these reasons, surgery should be delayed, if possible, for a period of time after PTCA. The length of time depends on the method of relieving the vessel obstruction. Table 127.2 outlines the management of the surgical patient following PTCA.[16]

Cardiac events following non-cardiac surgery have been reported to occur at rates of 1–5% and as high as 30% in vascular surgery.[19] Once a patient has been deemed medically appropriate to proceed with surgery, the consulting geriatrician must decide which interventions, in any, could modify perioperative risk and lower the chance of postoperative cardiac complications. One such intervention that has been highly debated is the use of perioperative beta-blocker therapy.

Currently, the ACC/AHA Guidelines recommend initiation of beta-blockers if evidence of cardiac ischaemia is found on preoperative testing or coronary disease and more than one cardiac risk is present in patients undergoing vascular or intermediate-risk surgeries. No recommendation (uncertain usefulness) is given for patients without evidence of ischaemia or with less than two cardiac risks.[16]

Table 127.2 Management of surgical patients after percutaneous coronary angiography (PTCA).

Procedure	Days post-PTCA			
	<14	14–29	30–365	>365
Balloon angioplasty	–[a]	Aspirin[b]	Aspirin[b]	Aspirin[b]
Bare metal stent	–[a]	–[a]	Aspirin[b]	Aspirin[b]
Drug-eluding stent	–[a]	–[a]	–[a]	Aspirin[b]

[a]Defer surgery.

[b]Proceed with surgery with aspirin alone as antiplatelet agent.

A 2005 meta-analysis evaluating cardioselective beta-blocker use in patients over the age of 65 years found an overall protective effect of beta-blocker therapy for perioperative cardiac mortality, long-term overall and cardiac mortality and myocardial infarction (MI) or ischaemia. The largest effect was seen for postoperative myocardial ischaemia with a number needed to treat (NNT) of 6.[19]

In 2008, another meta-analysis showed different results. Overall, use of perioperative beta-blockade was associated with a 35% decrease in non-fatal MI (NNT 63) and 64% decrease in myocardial ischaemia (NNT 16), but it was also associated with a 116% increase risk of non-fatal strokes and *no* reduction in all-cause or cardiovascular mortality.[20]

A large proportion of the data from the second meta-analysis was derived from the landmark PeriOperative ISchemic Evaluation (POISE) trial, which randomized over 8000 patients with or at risk for atherosclerosis to receive extended-release metoprolol or placebo. Patients already on beta-blockade were excluded. Treatment was initiated 2–4 h prior to surgery, titrated to 50% of maximum dose, and was continued for 30 days postoperatively. The researchers found that metoprolol administration was associated with a reduction in the rate of MI, cardiac revascularization and clinically significant atrial fibrillation; however, the same group had significantly more all-cause mortality, stroke, hypotension and bradycardia.[21] Critics of the POISE trial argue that the relatively high doses of metoprolol and initiation of therapy close to surgery (within hours) led to the high number of adverse outcomes.[22] Still, these findings have spurred much debate on the safety of perioperative beta-blocker use.

Currently, experts recommend continuation of beta-blockers in patients on long-term therapy. Additionally, based on studies examining beta-blockers started 30 days prior to surgery, one may consider initiation of low-dose therapy (2.5 mg per day of bisoprolol and 25 mg per day of metoprolol) well in advance (2–4 weeks) of planned, elective surgery.[22]

Other interventions to reduce risk of perioperative cardiac complications should be individualized based on the preoperative evaluation.

Pulmonary risk assessment

Much emphasis has been placed on perioperative cardiac risk assessment; however, postoperative pulmonary complications are as common (and, in some case series, more common) as cardiac complications and equally predict perioperative mortality.[4] A reduction in lung volume occurs during surgery, which in older patients compounds the age-related changes in the pulmonary system, leading to atelectasis and other complications. Clinically important pulmonary complications are pneumonia, atelectasis, bronchospasm, respiratory failure with prolonged mechanical ventilation and exacerbation of COPD.[4] Risk factors for pulmonary complications can be divided into patient-related and procedure-related.

Patient-related risk factors include COPD (most important patient-related factor, increasing risk by 3–4-fold), cigarette use (increases risk by threefold), smoking cessation in the 1–2 months prior to surgery, ASA class >2, poor exercise tolerance (measured by an inability to perform supine bicycle exercise test for 2 min), albumin levels $<3\,g\,dl^{-1}$ and blood urea nitrogen levels $>30\,mg\,dl^{-1}$.[4,14,23]

Procedure-related risk factors include type and length of surgery, long hospital stay, anaesthesia type (lower risk with spinal or epidural) and long-acting neuromuscular blockade (pancuronium).[4,14,23]

The single strongest predictor of postoperative pulmonary complications, outweighing all patient-specific factors, is surgical site.[4] Thoracic and upper abdominal surgeries (closest to the diaphragm) carry the highest risk. Neurological, peripheral vascular, abdominal aortic aneurism and neck surgeries also carry a high risk, presumably owing to the increased length of these procedures and a higher incidence of smoking and COPD in patients undergoing them.[4]

A multifactorial risk index for predicting postoperative respiratory failure has been developed; however, its use for risk reduction is limited by the fact that none of the factors are modifiable in the immediate preoperative period.[7] The utility of preoperative pulmonary function testing for predicting outcome and perioperative management is not supported by evidence and is not routinely recommended.[4]

Interventions to reduce risk of pulmonary complications can be effective. Preoperatively, pulmonary status should be optimized. If elective surgery is planned 8 or more weeks in advance, the geriatrician ought to encourage smoking cessation, teach lung expansion manoeuvres and refer for pulmonary rehabilitation with a focus on improving exercise capacity. If surgery is planned within 1–2 months, patients should not be encouraged to quit smoking, as this can actually increase the risk of postoperative pulmonary complications.[4,10] Exacerbations of COPD or asthma and lower respiratory tract infections should be treated prior to proceeding with surgery.

Intraoperative risk reduction strategies, such as shorter surgical durations and avoidance of pancuronium, require the consulting geriatric specialist to collaborate with the surgeon and anaesthesiologist.[4]

Postoperative risk reduction strategies focus on lung expansion. Incentive spirometry, deep breathing and early ambulation are simple, low-risk, inexpensive and effective methods to avoid atelectasis and pneumonia. Adequate pain control is essential to prevent splinting and maximize lung expansion manoeuvres.[4,10]

Neurocognitive risk assessment

Perioperative neurological complications are common in elderly surgical patients and include cerebral vascular accident or transient ischaemic attack, delirium and neurocognitive disorder. The most common is postoperative delirium (PD).[9,10] Neurological complications increase morbidity, mortality and length of hospital stay.[9,24]

PD is distinguished from postoperative cognitive disorder (POCD) in its time course and manifestation. Delirium is defined by acute, fluctuating changes in memory, consciousness and perception. It is identified using DSM IV or Confusion Assessment Method (CAM) criteria. The incidence of PD in the literature varies widely, from 3 to 61%, with increased incidence in orthopaedic and aortic surgeries.[10,15,24] Major factors predisposing to delirium are increasing age, mild cognitive impairment (MCI), frailty and dementia. Modifiable risk factors for PD include intraoperative blood loss, postoperative anaemia (haematocrit <30%), electrolyte imbalances, sepsis, use of a bladder catheter, physical restraints, poor postoperative mobility and polypharmacy.[10,15] Preoperative evaluation begins with cognitive assessment for MCI, dementia and preexisting delirium. Examples of assessment tools are given in other chapters of this book (see Section 7, Dementia and Cognitive Disorders, for more details on geriatric cognitive assessment). The geriatric consultant should then assess the patient for the presence of the modifiable risk factors listed above. Geriatrics consultation was shown to reduce PD in a group of elderly hip fracture patients.[25]

Using a structured protocol, a consulting geriatrician made individualized recommendations that addressed modifiable risks for PD. The results were compared with a control group who received usual care by the orthopaedic surgical team. The most frequently followed recommendations were transfusion to keep haematocrit >30%, removal of indwelling urinary catheters by postoperative day two and discontinuing or limiting the use of psychoactive medications. In the geriatric consultation group, no difference in delirium duration or length of stay was noted; however, there was a statistically significant reduction in the incidence of delirium with an NNT of 5.6.[25]

Multidisciplinary non-pharmacological interventions targeting modifiable factors have been shown to decrease delirium;[26] however, research continues in order to find effective pharmacological therapy for the prevention and treatment of PD. A blinded, randomized, placebo-controlled trial evaluated the use of low-dose haloperidol for prophylaxis against PD in a cohort of 430 hip surgery patients. The incidence of delirium did not differ between the groups; however, the severity was lower and duration of delirium and hospital length of stay were shorter in the group given haloperidol.[26] Unfortunately, this study was underpowered and further study is needed before recommendations can be made for pharmacological prophylaxis of PD.

In contrast to PD, POCD manifests days or weeks after surgery and is characterized by impaired concentration, language comprehension, social integration and ability to learn new information that can persist for months to years. The literature suggests a prevalence rate of 15–25% and is most common after coronary artery bypass grafting.[27] The exact aetiology of POCD is unclear, but some perioperative risk factors have been identified, including age, duration of surgery, lack of education, postoperative infection or inflammation, hyperglycaemia and hyperthermia.[10,28] Some evidence for cholinergic and dopaminergic imbalance has been suggested. Of note, general anaesthesia has *not* been associated with increased rates of POCD or PD.[27] Management of POCD has not been well established and largely focuses on supportive care.

Postoperative management of the geriatric patient

The role of the geriatric specialist to improve postoperative outcomes begins before surgery but continues until discharge. There are seven common postoperative problems that if not prevented or managed appropriately can lead to physical decline and poor outcomes (see Box 127.1).[29]

Immobility

Bed rest is bad. The multiple complications of immobility include ulcer formation, bone loss, muscle weakness, psychosocial decline, atelectasis, aspiration, urinary retention, constipation, venous thrombosis and orthostatic hypotension.[29] The effects are even more profound in patients who were frail prior to surgery. The effects of bed rest are easily counteracted by early mobility and rehabilitation. For mobilization to occur successfully, the entire medical team, including doctors, nurses and physical and occupational therapists, must formulate a rehabilitation plan and encourage patient participation.

Box 127.1 The 'Dirty Seven'

Seven barriers to a successful postoperative course

- Immobility
- Infection
- Venous thromboembolism
- Malnutrition
- Pain
- Ileus/constipation
- Urinary retention/incontinence

Infection

The three most common sites of postoperative infection in the elderly are urinary tract, surgical site and respiratory tract.[29] Interventions aimed at preventing infections should focus on those areas. To limit the rate of urinary tract infections, use of indwelling bladder catheters ought to be discouraged. If urinary retention is present, intermittent catheterization with mobilization and a commode toileting schedule is preferable. Aggressive pulmonary toilet and avoiding bed rest can decrease atelectasis and aspiration, which are significant risk factors for postoperative pneumonia. The surgical incision site needs to be examined frequently for signs of infection. Surgical site infections have been shown to increase mortality, hospital length of stay and cost in the elderly.[30] Close surveillance and adequate prophylaxis are particularly needed for patients coming from other healthcare facilities, including long-term care. In a group of elderly orthopaedic surgery patients, admission from a healthcare facility increased the risk of infection.[30] Antimicrobial prophylaxis should be administered 1 h prior to surgery and possibly continued 24 h postoperatively depending on surgical type The choice of antibiotic should be tailored to the institution's antibiogram to include appropriate coverage of the most common organisms.[29]

Venous thromboembolism

Several guidelines exist for the prophylaxis of venous thromboembolic phenomena (VTE). The most comprehensive guideline is from the American College of Chest Physicians (ACCP), last updated in 2008.[31] All surgical patients require prophylaxis against VTE. The type and duration of VTE prophylaxis depend on three factors: (1) surgical risk category, (2) presence of significant comorbid disease (e.g. cancer, renal insufficiency) and (3) bleeding risk. Tables 127.3 and 127.4 summarize the ACCP recommendations for perioperative VTE prophylaxis.[31,32]

Without prophylaxis, the rate of DVT in general surgery patients is estimated to occur at 10–40%; however, the incidence of DVT in orthopaedic surgery patients is much higher at 40–60%.[31] For this reason, the recommendation for VTE prophylaxis differs for orthopaedic patients. Table 127.5 gives a summary of the recommendations.[31,32]

Before initiating anticoagulation for VTE prophylaxis, an estimation of renal function is critical. Geriatric patients experience age- and disease-related reductions in renal function and creatinine clearance. It is essential to calculate creatinine clearance using the Cockroft–Gault or MDRD (Modification of Diet in Renal Disease) equation as creatinine levels may be deceptively normal. This is especially relevant for anticoagulant use as low-molecular weight heparins and fondaparinux are primarily renally eliminated. Reduced renal function leads to reduced drug clearance and increased serum drug concentrations.[32] Options for patients with renal insufficiency include the use of twice daily unfractionated heparin or reduced-dose enoxaparin (30 mg per day s.c.). Note that fondaparinux is contraindicated in patients with renal impairment.[32]

Table 127.3 Surgical risk categories for VTE.

Low risk	Minor or same-day surgery Age <40 years No additional VTE risk factors[a]
Moderate risk	Age <60 years Gynaecological or laparoscopic surgery ≤1 VTE risk factor[a]
High risk	General, colorectal, gynaecological, urological, bariatric or laparoscopic surgery Age >60 years ≥2 VTE risk factors[a]
Very high risk	Cancer surgery

[a]VTE risk factors include congestive heart failure, severe respiratory disease, immobility, active cancer and/or treatment for cancer, previous VTE, sepsis, acute neurological disease, inflammatory bowel disease, advanced age, obesity, central venous catheter and nephrotic syndrome.

Malnutrition

Presurgical nutritional status, classically assessed using serum albumin, predicts surgical outcomes in the elderly.[10] Preoperative optimization of nutrition with supplements may improve outcomes, but it is also important to ensure adequate nutrition postoperatively.[29] Registered dieticians can aid in assessing protein–calorie requirements and recommending appropriate supplementation.

Pain

For various reasons, elderly patients communicate pain less than younger patients, leaving them undertreated.[10] As mentioned previously, changes in the renal and neurological systems with ageing affect sensitivity to and serum concentrations of opioids. This has been shown to manifest as a decreased need for opioids several days following surgery in patients over the age of 70 years compared with younger patients. In the immediate postoperative period, however, the requirements are similar and intravenous doses of morphine and patient-controlled analgesia can be safely used.[10] For more information on the use of opioid medications in the elderly, see Chapter 135: End of life and palliative care

Table 127.4 Recommendations for perioperative VTE prophylaxis.

Risk category	Initiation	Duration	Prophylactic strategy
Low risk	Immediate	Indefinite	Early ambulation
Moderate risk	Within 12–24 h of surgery	7–10 days	Mechanical compression if bleeding risk Unfractionated heparin: 5000 U s.c. b.i.d. LMWH: Enoxaparin 40 mg per day s.c. Dalteparin 5000 IU per day s.c. Enoxaparin 60 mg s.c. b.i.d. (BMI $>50\,kg\,m^{-2}$) Factor Xa inhibitor: Fondaparinux 2.5 mg per day s.c.
High risk	Within 12–24 h of surgery	7–10 days	Unfractionated heparin: 5000 U s.c. t.i.d. LMWH: Enoxaparin 40 mg per day s.c. Dalteparin 5000 IU per day s.c. Enoxaparin 60 mg s.c. b.i.d. (BMI $>50\,kg\,m^{-2}$) Factor Xa inhibitor: Fondaparinux 2.5 mg per day s.c. Consider combination of anticoagulation and mechanical compression
Very high risk	2–12 h before or 12–24 h after surgery	$\geq$7–10 days with consideration to extend up to 4 weeks	Unfractionated heparin: 5000 U s.c. t.i.d. LMWH: Enoxaparin 40 mg per day s.c. Dalteparin 5000 IU per day s.c. Tinzaparin 3500 IU per day s.c. Factor Xa inhibitor: Fondaparinux 2.5 mg per day s.c. Consider combination of anticoagulation and mechanical compression

Table 127.5 Recommendations for VTE prophylaxis in the orthopaedic surgical patient.

Type of surgery	Duration	Prophylactic strategy
Knee arthroscopy	Throughout hospital stay	Early ambulation LMWH if additional VTE risk factors are present
Hip fracture repair	10–35 days Initiate preoperatively if surgery delayed	LMWH: Enoxaparin 40 mg per day s.c. Enoxaparin 30 mg s.c. q12 Dalteparin 5000 IU per day s.c. Factor Xa inhibitor: Fondaparinux 2.5 mg per day s.c. Unfractionated heparin 5000 U s.c. b.i.d. or t.i.d. Adjusted-dose warfarin to INR 2.0–3.0
Total hip replacement	10–35 days	LMWH: Enoxaparin 40 mg per day s.c. Enoxaparin 30 mg s.c. q12 Dalteparin 5000 IU per day s.c. Factor Xa inhibitor: Fondaparinux 2.5 mg per day s.c. Adjusted-dose warfarin to INR 2.0–3.0
Total knee replacement	10–35 days	LMWH: Enoxaparin 30 mg s.c. q12 Factor Xa inhibitor: Fondaparinux 2.5 mg per day s.c. Adjusted-dose warfarin to INR 2.0–3.0

Constipation and ileus

Abdominal surgeries, bed rest and poor oral intake all contribute to ileus and constipation. For non-intestinal surgeries, bowel function should be stimulated early to prevent complications. Non-pharmacological strategies include mobilization and increase in fluid intake.[29] Pharmacological strategies include the use of stimulant laxatives. Stool softeners, such as docusate, do not work to stimulate bowel function postoperatively and are not recommended.

Urinary retention and incontinence

Urinary retention and incontinence are not normal signs of ageing. They can occur as a consequence of surgery-related factors, such as immobility, anticholinergic medications, postoperative delirium, indwelling catheters, faecal impaction and urinary tract infection. These causes should be investigated when abnormal urination occurs following surgery. A scheduled toileting plan should be instituted along with avoidance of indwelling catheters and early mobilization.[29]

Conclusion

Comprehensive perioperative management of the geriatric patient is crucial as the population ages and requires more surgical interventions. The perioperative course can be improved with geriatric consultation. Ideally, preoperative assessment and management would begin months in advance of elective surgery to improve premorbid functioning and minimize comorbid conditions. Smoking cessation, nutritional supplementation and improvement in exercise tolerance can all reduce the impact of age-related disease states on postoperative outcomes. Preoperative cardiac, pulmonary and neurological assessments can help identify patients at high risk of related complications and interventions aimed at reducing risk can be instituted. Postoperative problems can be prevented or ameliorated by early mobility, adequate pain control, toileting schedules, VTE prophylaxis and medication review. A multidisciplinary approach is necessary for successful implementation of risk-reduction strategies in the elder surgical patient.

Key points

- Focus on improving premorbid functioning prior to surgery.
- Smoking cessation improves outcomes.
- Peri- and postoperative involvement of a geriatrician can improve outcomes.

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CHAPTER 128

Anaesthesia

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Introduction

Elderly surgical patients present a specific challenge to anaesthesiologists and may be at greater risk of an adverse outcome.[1] This is accounted for by a reduced ability to maintain or restore physiological homeostasis in the face of surgical and medical disease. This is exacerbated further by the presence of medical comorbidity such as cardiac or pulmonary disease or diabetes mellitus.[2] The statistical likelihood of having a coincident medical pathology increases with advancing years. The elderly have a higher rate of mortality associated with anaesthesia and surgery than their younger counterparts. Postoperative adverse events on the cardiac, pulmonary, renal and cerebral systems are the main concerns for older surgical patients at high risk. The very fact that the patient requires hospital admission for their surgery exposes them to risk, with familiar hazards including nosocomial infection, administration of the wrong drug and side effects of certain procedures and investigations. Elderly patients are more likely to experience an adverse event during their hospital stay. The reduction of iatrogenic injury is one of the stated aims of the World Health Organization.[3]

The elderly, in particular those older than 85 years, are the fastest growing segment of the European and North American populations.[4] Accordingly, overall life expectancy and active life expectancy have increased.[4] The number of older patients presenting for surgery and anaesthesia is increasing and should not be a bar to surgery.[5] The complexity of surgical procedures is also expanding. In 2001, the Association of Anaesthetists of Great Britain and Ireland called for this expansion to be recognized and incorporated into service provision. They also called for greater availability of 24 h recovery facilities, High Dependency Unit (HDU) and Intensive Therapy Unit (ITU) beds for these patients.[6]

The National Confidential Enquiry into Perioperative Deaths[7] highlighted the importance of availability of high dependency and intensive care facilities for the safe care of older patients: 'the decision to operate includes the commitment to provide appropriate supportive care'.

This chapter elaborates on some of the risks to the elderly patient during the perioperative period and how they may be managed in order to minimize postoperative morbidity and mortality in this vulnerable patient group.

Outcome of surgery and anaesthesia in the elderly

Mortality after surgery and anaesthesia is defined as the death rate within 30 days.[7] The outcome of older patients from surgery, in general terms, has been studied by several groups in the past two decades,[8–10] suggesting that healthcare practitioners have anecdotally identified areas for potential clinical improvement for many years. However, there are no recent surgical outcome studies for older patients. These early studies suggest that older patients have acceptable rates of perioperative mortality. There have been many advances in surgery and anaesthesia, such as laparoscopic surgery, ultra-short-acting anaesthetic medications, regional pain management and more extensive use of critical care services, over the past two decades, reducing mortality rates (Table 128.1, Figure 128.1). Higher mortality rates are associated with higher American Association of Anesthesiologists (ASA) grade of physical status grade and emergency procedures.[11] ASA is an independent predictor of mortality (Table 128.2). The highest risk surgical procedure in older patients is an exploratory laparotomy, because of the high risk of bowel infarction and disseminated carcinomatosis.

The presence of preoperative renal, liver and central nervous system impairment was a predictor of poorer outcome. Albumin, a marker of nutritional status, may serve as a surrogate marker for the preoperative health status of the surgical geriatric patient.[12]

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Table 128.1 Mortality associated with surgery and anaesthesia.

Age (years)	Mortality rate (%)	Ref.
General population	1.2	13
60–69	2.2	13
70–79	2.9	13
>80	5.8–6.2	10
>90	8.4	9
>95	13	10

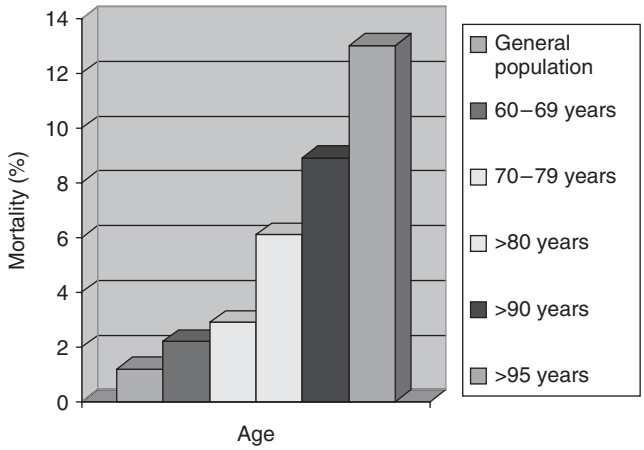

Figure 128.1 Mortality associated with surgery and anaesthesia.

Table 128.2 ASA grading of physical status.[11]

Grade	Status
I	Normal healthy patient
II	Patient with mild systemic disease
III	Patient with severe systemic disease
IV	Patient with severe systemic disease which presents a constant threat to life
V	Moribund patient not expected to survive without operation

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Cardiovascular morbidity associated with surgery and anaesthesia

The age-related changes that occur within the cardiovascular system are responsible for the higher incidence of perioperative myocardial infarction, cardiac failure and arrhythmias in this age group. There is a reduction in the sensitivity of the parasympathetic system to changes in baroreceptor stretch, blood pressure and heart rate. The sensitivity of the sympathetic system also declines. This diminishes the body's ability to compensate for sudden change. There is a progressive stiffening of both the arterial and venous vessels, again reducing capacity for vasoconstriction or dilatation in the face of loss of intravascular volume. Stiffening of the myocardium also occurs, affecting diastolic relaxation and filling pressures. This may lead on to diastolic dysfunction with an increase in left atrial pressure and pulmonary congestion.

Superimposed on physiological change, anaesthetic agents cause peripheral vasodilatation, with a decrease in systemic vascular resistance. As many elderly patients have a contracted intravascular volume secondary to diuretic therapy, this can mean a sudden fall in tissue perfusion pressure. Anaesthetic agents are myocardial depressants, particularly in higher doses, and have the capacity to affect cardiac output adversely. Preoperative assessment is focused on identifying those risk factors that have been identified in studies as being predictive of adverse postoperative outcome (Table 128.3).[13,14] Following the initial interview, the patient's baseline level of function is assessed. If there are no significant predictors in the history, evaluation may be safely confined to detailed physical examination and a 12-lead electrocardiogram (ECG). The ECG will identify patients with left ventricular hypertrophy or ST segment depression. These patients may require further investigation with an exercise ECG, depending on the surgical procedure planned. Determination of the anaerobic threshold for each patient using cardiopulmonary exercise testing is now considered a sensitive tool for determining patients at high risk.[15] Patients who cannot exercise because of claudication or arthritis may be assessed with a dobutamine stress echocardiograph. Coronary angiography is reserved for patients with angina at rest or unstable angina. On the basis of the results, preoperative revascularization may be warranted. Clinically detected cardiac murmurs and features of congestive cardiac failure are further evaluated using echocardiography.

Preoperative valve replacement is indicated for patients with severe disease. Less severe valve lesions or those

Table 128.3 Predictive factors for postoperative cardiovascular morbidity.

Myocardial infarction within previous 3 months
Decompensated congestive cardiac failure
Arrhythmia (except premature atrial contractions)
Unstable angina or angina at rest (New York Heart Association Grade IV)
Uncontrolled hypertension
Severe valvular disease
Poor general medical condition
Poor exercise capacity
Diabetes mellitus
History of stroke

following valve surgery require prophylactic antibiotic administration. Arrhythmia detected at rest or during exercise should be treated if possible before surgery. If sinus rhythm is not achieved, rate control with anticoagulation is acceptable. Type II or type III heart block requires insertion of a temporary or permanent pacemaker. Using the information gained from the history, examination and further investigations, the anaesthetic management is aimed at maximizing myocardial perfusion through maintenance of tissue perfusion pressure and oxygenation throughout the intra- and postoperative period. Postoperative admission to the HDU or intensive care unit (ICU) should be anticipated for elderly patients with significant cardiac symptoms, especially those undergoing abdominal or thoracic procedures. Invasive monitoring of blood pressure and central venous pressure is commenced early and continued throughout the perioperative period. Regional anaesthesia provides superior analgesia postoperatively and may reduce the incidence of adverse cardiac events in certain patients, such as vascular and abdominal surgery. The institution of perioperative β-receptor blockade has been shown to reduce the risk of myocardial ischaemia and is generally well tolerated by older patients.[16] β-Blockade is thought to increase the time spent in diastole, increasing filling and increasing time for coronary artery perfusion. A combination of intravenous fluid infusion and vasopressor agents is used to maintain mean arterial blood pressure within 20% of the patient's baseline, awake blood pressure. Episodes of hypotension must be managed promptly and oxygenation increased during the period of reduced flow.

Postoperatively, the patient requires a similar level of care and monitoring. Supplemental oxygen therapy, optimum analgesia, rate control and judicious blood transfusion will assist in maximizing myocardial oxygen supply. Particular attention should focus on the first 3 days, when myocardial infarction is most likely to occur. Many episodes of ischaemia in this age group may be silent and may not be associated with the development of Q waves on the ECG. A low index of suspicion, the presence of new ST changes, in combination with serial estimations of serum troponin T and I concentrations, will assist in early diagnosis.

Respiratory morbidity associated with surgery and anaesthesia

The physiological changes associated with ageing predispose the older patient to respiratory complications after surgery and anaesthesia. A mixed obstructive–restrictive pattern develops from the decrease in total lung capacity, elastic recoil of the thorax, pulmonary parenchymal compliance and vital capacity. Decreased compliance and muscle power mean a fall in forced expiration and a reduced capacity to cough and clear secretions. Closing capacity, dead space and residual volume increase so that the lungs of the supine patient become atelectatic. These changes do not occur in a uniform manner throughout the lungs, resulting in areas of good ventilation in combination with underventilated segments. A decrease in pulmonary blood flow combined with progressive loss of alveolar surface area diminishes the resting arterial oxygen tension from 95 ± 2 mmHg at age 20 years to 73 ± 5 mmHg at age 75 years. Occurring in tandem, there is an age-associated loss of central nervous system sensitivity to changes in arterial oxygen and carbon dioxide tensions. The physiological and structural changes cause an increase in ventilation–perfusion mismatch. This is exacerbated by the effect of anaesthesia, in particular, general anaesthesia. In addition, general anaesthesia reduces reflex pulmonary hypoxic vasoconstriction. Regional anaesthesia impacts less on the respiratory system as it does not necessitate intubation of the trachea, avoids the effect of intermittent positive pressure ventilation and provides highly effective postoperative pain relief.

Preoperative preparation of the patient involves a detailed history and examination in combination with functional assessment. Taking the patient for a walk, including two flights of stairs, during the preoperative visit provides a useful measure of the patient's baseline physiological status. Smoking cessation for at least 8 weeks is to be recommended.[17] Chest physiotherapy in the 24 h preceding surgery provides some physical benefit and facilitates instruction for deep breathing and coughing postoperatively. Patients with active pulmonary infection require more postponement of surgery and more aggressive medical treatment. The anaesthetic technique should employ regional analgesia/anaesthesia where possible. Short-acting agents such as propofol, remifentanil, sevoflurane and atracurium are most suitable for general anaesthesia. Muscle relaxants should always be reversed at the end of the procedure. Invasive monitoring may be used to advantage to guide fluid therapy as the older patient will tolerate rapid expansion of intravascular and extravascular volumes poorly due to the changes in pulmonary compliance, perfusion and renal function. This may be continued into the postoperative period in the context of ICU or HDU admission. Postoperatively, oxygen supplementation and chest physiotherapy should be continued for a minimum of 5 days as this is the greatest period of risk of nocturnal hypoxia and the onset of pneumonia.

Central nervous system morbidity associated with surgery and anaesthesia

Elderly patients are at risk of serious central nervous system morbidity and mortality due to neuronal loss associated with ageing, the presence of coincident pathology

such as cerebrovascular atherosclerosis and a reduction in neurotransmitter concentrations. This makes them less able to adapt successfully to the challenges imposed by surgery and anaesthesia. The morbidity associated with anaesthesia and surgery in the older patient most commonly takes the form of postoperative confusion (POC) or stroke.

Postoperative confusion

The risk factors for the development of POC are listed in Table 128.4. POC is associated with an increased rate of morbidity, delayed return to baseline function and delayed discharge home from hospital. To date, there is little evidence for an overall strategy to reduce the incidence in surgical patients, but some general recommendations may be made.

Consideration should be given to admitting the patient as a daycase, as elderly patients become less disorientated when in familiar surroundings with familiar carers. The preoperative assessment should highlight particular issues that could be modified or pre-empted, such as alcohol withdrawal depression. Hearing aids and spectacles should be left with the patient until induction of anaesthesia and returned to the patient as soon as possible. Medications listed in Table 128.3 should be avoided. Intraoperative monitoring of blood pressure, ventilation and oxygenation requires a meticulous approach.

Hypoxaemia and hypercarbia should be avoided. The minimum number of medications possible should be employed. Regional analgesic techniques should be employed where possible to reduce the use of sedating narcotics in the postoperative period. There is no difference in the incidence of POC between the intraoperative use of general anaesthesia and spinal or epidural anaesthesia.[18] A geriatrician should be involved in the care of the patient at high risk of confusion. Postoperatively, if the patient is confused, they should be nursed in a quiet, dark room. Organic causes should be treated promptly. Haloperidol 0.25–2 mg orally at night may be useful. Low doses of diazepam or chlorpromazine may be used as adjuncts if the patient does not respond to simple measures. Physical restraints usually serve to antagonize the patient further and should not be used. Referral to the occupational therapy and social work departments will be necessary to assist with cognitive assessment, follow-up and discharge planning.

Long-term cognitive impairment has been documented by the International Study of Postoperative Cognitive Dysfunction (ISPOCD).[19] About 10% of patients were found to have cognitive deficits 3 months after surgery, with age as the only significant predictive factor.

Table 128.4 Risk factors for the development of postoperative confusion.

Preoperative factors
Older age
Depression/anxiety
Dementia
Preoperative sensory deficit in hearing or vision
Alcohol withdrawal/sedative withdrawal
Preoperative use of multiple medications
Intraoperative factors
Hypoxia
Hypocarbia
Hypotension
Postoperative factors
Inadequate analgesia
Perioperative factors
Sepsis
Surgical procedure
Cardiac surgery
Orthopaedic surgery, especially joint replacement
Perioperative medications
Anticholinergics: atropine, scopolamine. Glycopyrrolate to a lesser extent
Barbiturates
Benzodiazepines
Antihistamines

Postoperative stroke

There have been few studies to determine the incidence of stroke occurring after surgery and anaesthesia. The incidence from small retrospective studies seem to suggest that the incidence is low, in the order of 0.25% when a patient is undergoing non-carotid vascular surgery.[20] Stroke most commonly occurs between days 5 and 26 postoperatively. Risk factors for postoperative stroke are given in Table 128.5.[21]

Patients with poorly controlled preoperative hypertension should have their surgery postponed to allow time to institute adequate pharmacological control. Patients with clinically detected carotid bruits should have further investigations and, if necessary, referral to a vascular surgeon before their intended procedure. The severity of the neurological deficit and the potential for rehabilitation after perioperative stroke vary enormously and therapy must be directed at the individual patient.

Renal morbidity associated with surgery and anaesthesia

Renal function is known to deteriorate with age and, therefore, greater care will be needed to maintain renal function perioperatively. Decline in numbers of the functional unit, the glomerulus, with age means that glomerular filtration

Table 128.5 Risk factors for postoperative stroke in the elderly.

Preoperative factors
Pre-existing cerebrovascular disease
Ischaemic cardiac disease
Atherosclerosis
Carotid occlusion
Preoperative vascular disease
Hypertension
Diabetes mellitus
Physical inactivity
Intraoperative and postoperative factors
Haemodynamic instability
Hypoxaemia

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rate (GFR) falls from 125 ml min^{-1} in the young adult to 80 ml min^{-1} in the older individual. As this fall in GFR is usually accompanied by a decrease in muscle mass, there is rarely an increase in serum creatinine. During the perioperative period, the kidney will be exposed to many challenges: rapid fluid shifts in the intravascular and extravascular compartments, numerous medications administered simultaneously, electrolyte changes and acid–base abnormalities. In the face of these challenges, the underlying loss of function becomes exposed, leading to the development of postoperative renal failure. Atherosclerosis of the vascular supply of the kidney and coincident disease due to diabetes mellitus or hypertension further complicate the situation. In addition, the elderly patient tends to be taking a greater number of prescribed medications that have the potential to interact with anaesthetic agents and conditions arising during surgery, such as hypotension. Anaesthetic drugs have little direct effect on renal function. Anaesthetic agents reduce cardiac output with subsequent renal vasoconstriction, which may cause a fall in renal perfusion. Enflurane and isoflurane produce fluoride when metabolized, which may cause renal injury if the anaesthesia is very prolonged. Sevoflurane produces a substance known as compound A at low fresh gas flows, which is nephrotoxic if not removed by effective scavenging of waste anaesthetic gases.[22] It is unusual for either of these chemical entities to present a problem in the clinical context.

Management of the patient starts with a high index of suspicion. Following a detailed preoperative review, fluid and electrolyte status should be closely monitored in the pre-, intra- and postoperative periods. Nephrotoxic medications should be stopped preoperatively if possible. Medications that deplete the intravascular volume and lead to electrolyte loss should be reviewed in the context of the patient's state of hydration and the planned surgical procedure. For example, a patient taking a loop diuretic scheduled for elective inguinal hernia repair should probably continue taking the medication, whereas a patient with low urinary output scheduled for emergency laparotomy for bowel obstruction should have the loop diuretic reviewed by the anaesthesiologist. The dosing intervals of medications excreted by the kidney such as aminoglycosides may need to change and doses titrated to plasma levels. The development of perioperative renal failure increases the requirement for renal replacement, intensive care admission and mortality. Acute tubular necrosis accounts for the majority of cases of renal failure. Prevention is based on optimizing the circulation preoperatively, close haemodynamic monitoring perioperatively and maintenance of adequate perfusion pressures, including the judicious use of inotropes. Intraoperative low-dose dopamine infusion promoting renal vasodilatation and the use of mannitol as a free radical scavenger have been advocated.[23,24]

Perioperative hypothermia

Elderly patients are at a greater risk of developing perioperative hypothermia than younger patients, owing to a number of factors. They have a reduced muscle mass, with a lower basal metabolic rate. This is often accompanied by reduced fat stores secondary to malnutrition. The shivering mechanism occurs later in response to cooling. In young patients, shivering begins peripherally at 1°C less than the normal core temperature of 36.5°C. As patients age, this may not occur until their core temperature has fallen by 2°C. Shivering increases cellular oxygen demands by 20–30%, increasing myocardial oxygen consumption, which may be deleterious for the older patient with cardiovascular pathology. Less vasoconstriction occurs in the older patient for a given fall in temperature, meaning that more heat is lost to the environment.

Surgery and anaesthesia have a detrimental effect on thermoregulation. Anaesthetic agents cause peripheral vasodilatation with abolition of the shivering mechanism so that patients lose the ability to compensate for cooling. The opening of major cavities such as the abdomen and thorax increases the amount of heat lost to the environment. The effects of perioperative hypothermia are listed in Table 128.6. Prevention of hypothermia is more efficient and cost-effective than warming the patient postoperatively. Patients should be kept in a warm room with blankets during their admission to the operating department. Induction of anaesthesia should take place in a similar environment. Anaesthetic gases should be warmed and humidified.

Intravenous fluids should be warmed. Sterile preparation of the operative site should take place using warmed sterile solutions. A warm ambient temperature of the operating room should be maintained until the patient is draped. Forced air warming blankets may be placed under the

Table 128.6 Effects of perioperative hypothermia.

- Increased cardiac morbidity
- Increased incidence of cardiac arrhythmias
- Altered platelet function
- Increased blood loss
- Increased blood viscosity – combined with vasoconstriction may cause a higher incidence of deep venous thrombosis
- Shift of oxygen dissociation curve to the left with less oxygen released by haemoglobin to the tissues
- Inhalation of cold gases causes reduction in protective reflexes in the respiratory tract through effects on cilia motility
- Increased incidence of postoperative wound infection
- Increased incidence of postoperative decubitus ulcers
- Decreased drug metabolism, resulting in longer recovery times
- Prolonged hospitalization

drapes. At the end of the procedure, warm blankets should be placed over the patient during their transfer to the post-anaesthetic care unit.

Preoperative assessment

When carrying out a preoperative assessment of the older patient, it is important to place the function of the cardiovascular and respiratory systems into the context of the whole patient. It must be remembered that patients may have mild cognitive impairment affecting their memory or they may be embarrassed and unwilling to admit disability. Answers may be slow as information is recalled. The history may be extensive and complicated and so sufficient time should be allotted to the interview. The clinical presentation of disease may differ greatly from that in younger patients. Conditions such as hyper- and hypothyroidism are notoriously difficult to diagnose in the older patient. It is best if the assessment takes place several days before the planned surgery to allow enough time for further investigations if necessary.

Attendance at a preanaesthetic outpatient clinic will mean that the patient can meet all of the multidisciplinary team members together, providing enhanced perioperative and discharge planning. Following the interview, the anaesthesiologist must review the patient's medical chart and carry out a comprehensive physical examination. Keeping in mind the demands and implications of each surgical procedure, the anaesthetic plan will then be made and discussed with the patient. The anaesthesiologist should expect much variation between each elderly patient. Routine investigations based on age alone are not warranted and should be directed by the clinical evaluation.[25]

Particular issues to be addressed over the course of the assessment are the following:

1 The planned surgery.

2 The cognitive status of the patient. Does the patient answer questions in a coherent manner? Will they be suitable for ambulatory admission or a regional anaesthetic technique?

3 The baseline function of the patient. Can they dress themselves, do the shopping, walk up a short flight of stairs?

4 Does the patient have symptoms suggestive of cardiac disease? Remember, patients may not report symptoms because of reduced mobility.

5 Does the patient have signs or symptoms of respiratory disease? Shortness of breath at rest is an important prognostic sign.

6 What are the patient's current medications and their compliance with them?

7 Previous anaesthetic experiences.

8 Vital signs on examination, especially blood pressure, pulse rate and rhythm.

Meticulous attention to detail when planning the perioperative care of the patient can reduce the incidence of minor morbidity. Reduction of minor incidents may prevent escalation into life-threatening events.

Pain assessment and management in the elderly

Pain assessment

Effective pain management in the elderly is subject to all of the usual barriers to pain management, such as fear of addiction. With the older surgical patient, there are additional problems to be overcome. The assessment of pain forms the basis of successful pain relief. It is necessary to obtain a baseline measure of pain before instituting pharmacological measures to reduce that pain. Assessment allows the treatment to be evaluated and the need for further pain relief established.[26]

Conventional pain scores such as the visual analogue score (VAS) have limited application in this age-group due to the prevalence of mild/moderate cognitive impairment, hearing difficulties and poor eyesight. The older patient may differ significantly in their cultural interpretation of pain and pain relief.[27] Reporting of pain may be altered in this age group because of the misperception among older patients that it is necessary for pain to follow surgery and that staff are doing all that they can to relieve it. They may also fear reporting that they have pain in case this means something has gone wrong or that they may be seen as being 'difficult'. Healthcare staff may mistake patients who do not report pain for patients who do *not* have pain. Attempts have been made to validate other scoring systems in older adults, but at present there is no single system suitable for all elderly patients.[28] The accuracy of pain assessments may be increased by making the assessment more frequently, particularly following the administration of each analgesic dose. Another hurdle to achieving adequate pain relief is

the assumption that elderly patients do not experience pain to the same extent as younger patients. There is very little evidence for this misperception.[29]

Effect of pain in older surgical patients

The consequences of pain in surgical patients include the following:[30]

- sympathetic hyperactivity, producing tachycardia, myocardial ischaemia, hypertension via the adrenal hormonal axis;
- decreased pulmonary function with atelectasis and hypoxaemia, as a result of poor cough and reduced mobility;
- increased risk of deep venous thrombosis (DVT), as a result of reduced mobility;
- potential development of a chronic pain state through sensitization of pain pathways;
- postoperative delirium, which is particularly the case in patients who have predisposing risk factors for delirium such as visual, hearing or cognitive deficit;
- increased length of stay.

Adequate pain relief in all patients may reduce postoperative morbidity.[30] The preoperative assessment visit should be used as an opportunity to discuss with the patient the postoperative analgesia pertinent for their procedure, particularly when regional analgesic techniques are planned. Education and reassurance may be provided to the patient and their family, diminishing their concerns regarding addiction and side effects. Instruction may be given on the use of equipment for patient-controlled analgesia (PCA), which may be reinforced later by a visit from the acute pain team.

Pharmacological management of pain

A continuous, multimodal approach to postoperative pain management is indicated for elderly patients because it minimizes potential adverse effects from high doses of any single agent. Changes in drug absorption, distribution, metabolism and elimination may affect the eventual plasma level and effect of a given analgesic drug. Increased gastric pH and decreased gastric motility reduce or delay drug absorption. The volume of distribution of drugs changes because of an increase in total body fat and a decrease in body water. Water-soluble opiates such as morphine have a smaller volume of distribution and therefore can produce higher plasma levels. Lipid-soluble drugs, such as fentanyl, have a larger volume of distribution and can produce a prolonged duration of action in older patients. Reduced serum albumin concentrations and other plasma proteins from chronic illness or poor nutrition will reduce drug distribution, increasing the potential for adverse affects. Concurrent medical conditions, for example, renal impairment, may reduce excretion of the drug from the body. Liver disease may reduce drug metabolism and lead to accumulation of active drug and active drug metabolites.

Reduced muscle mass leads to unpredictable absorption of drugs administered by the intramuscular route. The pharmacological analgesic options available are listed in Table 128.7. The key to effective pain management in patients of all ages is regular and appropriate assessment, combined with regular administration of multimodal analgesic agents.

The role of regional analgesia

The intraoperative use of regional anaesthetic techniques either in combination with general anaesthesia or alone has been shown to reduce short- and long-term mortality in the elderly following total hip arthroplasty, vascular surgery and abdominal surgery. It is thought to do this by sympatholysis, attenuating the stress response and improving myocardial oxygenation. Regional analgesia continued into the postoperative phase provides more profound analgesia with lower doses of narcotics than intravenous opioid administration, thus minimizing the potential for sedation, respiratory depression and ileus. It decreases the incidence of respiratory complications in patients undergoing abdominal and thoracic procedures and decreases admission rates to the intensive care unit and overall length of stay. Regional analgesia decreases the rate of postoperative DVT due to relative vasodilatation of the venous plexus in the lower limbs and by decreasing the time to mobilization. Continuous epidural analgesia postoperatively can cause hypotension and lower extremity motor and sensory deficits. For this reason, nursing and medical staff require training in the recognition and management of potential complications of regional analgesic techniques.

The role of patient-controlled analgesia (PCA) in the elderly

Intravenous PCA has been shown to be safe in elderly patients,[31] but healthcare staff frequently hesitate to prescribe it because of the concern that it may cause confusion or inadequate analgesia in the older patient. Older patients should not be automatically excluded from using PCA, via either the intravenous or the epidural route. The cognitive state and physical abilities of each patient should be assessed on an individual basis.

Ethical considerations for perioperative care of the elderly

Decisions regarding surgery and anaesthesia become more complicated in the older patient, particularly when their ability to make a competent decision is compromised

Table 128.7 Pharmacological analgesic options.

Agent	Advantages	Side effects
Acetaminophen (paracetamol)	Oral, intravenous and rectal routes Opioid sparing	Hepatotoxicity, do not exceed 4 g per 24 h
NSAIDs[a]	Oral, rectal, and parenteral routes Opioid sparing	Gastric irritation Renal toxicity Antiplatelet effects
COX-II[a] inhibitors	Oral and parenteral routes Opioid sparing	Gastric irritation Renal toxicity Less severe gastric irritation and renal toxicity than NSAIDs Possible cardiac effects
Opioids	Oral, rectal, parenteral, spinal and epidural routes Profound analgesia Available as short- and long-acting preparations	Sedation/confusion/dysphoria Respiratory depression Metabolites may be toxic, e.g. normeperidine Nausea/vomiting Ileus Pruritus Urinary retention when administered into CSF/epidural space Bradycardia Hypotension, especially if patient is dehydrated

[a]NSAID, non-steroidal anti-inflammatory drug; COX-II, cyclooxygenase-II.

through cognitive impairment or illness. Paternalism on the part of the physician does not respect the patient's fundamental right to autonomy. Patients must be provided with the information they require, in a suitable format, to empower them with decision-making capacity. Informed consent leading to the choice of a treatment option or informed refusal of a treatment option must be respected by all professionals. If there is concern regarding the older patient's ability to assimilate information and decide, then further advice should be taken before deeming the patient 'incompetent'. Formal assessment of mental state may be necessary. If legal incompetence is concluded, decisions about the cessation or instigation of treatment may be taken by a proxy. This is often a family member. However, it may not be valid to assume that the proxy knows the wishes of a patient as they may never have discussed issues such as withdrawal of treatment. The proxy may be appointed on a formal basis through enduring power of attorney or the patient may make their wishes known through an advanced directive. The legal standing of advanced directives varies across legal jurisdictions. If there is no proxy available, doctors may make decisions about care 'in the best interests' of the patient. Efforts should be made early in the patient's admission to anticipate important decisions about medical care so that the patient may be involved as much as possible and proxy decision-making is avoided. The patient's current and potential quality of life may impact on the decision to proceed to surgery or not.

Previously made decisions concerning resuscitation, often referred to as do-not-resuscitate (DNR) orders, should be revised before a patient is admitted to the operating department for surgery. The outcome of cardiac arrest differs greatly from that on the general ward, with 60% of patients surviving to hospital discharge compared with 7–17% of patients who sustain cardiopulmonary arrest on the ward.[32] This because cardiac arrest in the operating theatre is monitored and witnessed, whereas a patient may be arrested on the ward for a variable length of time before resuscitation efforts begin. In addition, cardiac arrest in the operating theatre is often due to reversible causes such as arrhythmia, medication administration or hypovolaemia, which, when promptly managed, restore adequate circulation to the patient. In the light of this, a patient with a terminal process such as pancreatic cancer, with a DNR order on the ward, may have this decision reversed during the period they are in the operating theatre for palliative ileostomy, if that is what the patient wishes following informed consent.

Strategy to reduce postoperative morbidity and mortality in the elderly

Reductions in anaesthesia- and surgery-related morbidity and mortality involve a strategy that encompasses both individual organ systems and a wider view of the perioperative process (Table 128.8).

Table 128.8 Summary of the anaesthetic management of elderly patients.

Preoperative assessment for identifying high-risk patients
Careful history
Physical examination
12-lead ECG
Functional status assessment
Nutrition assessment
Preoperative preparation
Effective control of coexisting disease
Stopped smoking for 8 weeks
Training in cough and lung expansion techniques
Chest physiotherapy for elderly at risk of pulmonary complications
Correction of malnutrition
Routine precautions for major surgery
Temperature monitoring and control
Ripple mattress
DVT prophylaxis
Intra-arterial pressure monitoring
Haemodynamic stability
Combination of anaesthetic and vasopressor, β-blockers and vasodilatation
Avoid fluid overload
Quick recovery from anaesthesia
Use short-acting anaesthetic agents
Combine epidural anaesthesia with GA for major abdominal and thoracic surgery
Antagonize neuromuscular blocking drugs
Postoperative period
Prevent hypoxaemia: supplemental oxygen, reversal of neuromuscular drugs
Prevent hypothermia: keep warm perioperatively
Effective postoperative pain control: regular multimodal analgesia

Preoperative nutritional supplementation

Up to 40% of older patients admitted to hospital are malnourished.[33] Elderly patients with malnutrition are poor candidates for surgery and anaesthesia, as it places them at particular risk from hypothermia, decubitus ulcers, drug overdose, local and systemic infection, anaemia and wound breakdown. The most common form of malnutrition in this age group is protein–calorie malnutrition. Low protein intake is associated with low intakes of calcium and vitamin D, both of which are necessary in the formation of callus after fracture. Loss of muscle secondary to malnutrition increases fatigability, decreases strength and reduces the ability to maintain adequate ventilation. The evidence from various studies, including a Cochrane review,[34] suggests that nutritional supplementation should be confined to those patients who are malnourished, in order to achieve an acceptable risk–benefit ratio, where side effects to the patient are balanced against a demonstrable clinical effect. The evidence to date suggests that simple oral supplements are the optimum method of supplementation as oral supplementation is more cost-effective, more tolerable and psychologically more acceptable to patients than nasogastric or parenteral nutrition. It has not been extensively studied, however. Simple qualitative assessment of nutritional status on admission to hospital may be carried out as part of the routine nursing assessment. Because of the prevalence of poor nutrition in older patients presenting for surgery, prompt preoperative referral to a dietician of all patients who are deemed malnourished on nursing assessment should take place. This will facilitate early institution of simple oral supplementation in the postoperative phase, with nasogastric supplementation in patients who are severely malnourished. The emphasis should be on restoring function and decreasing perioperative morbidity rather than rapid weight gain.

Prevention of perioperative decubitus ulcers

The older surgical patient presents a unique challenge to the perioperative care team in the prevention of pressure ulcers. It is suggested that 25% of pressure ulcers are acquired intraoperatively. For many patients, pressure ulcers mean increased pain, longer hospital stays and reduced quality of life. A pressure ulcer can be defined as an area of localized damage to the skin and underlying tissue, caused by a disruption in the blood supply, preventing oxygen and vital nutrients from reaching the cells.[35] A pressure sore begins in the operating theatre, developing initially in muscle and the subcutaneous tissues before progressing outwards to the dermis and epidermis. This causes an erythematous area, which may be mistaken for a burn. This may go on to become an established pressure sore. Pressure sores occurring in surgical patients are often not attributed to their time spent in theatre, as the initial damage may not be apparent until several hours or days have passed.

The development of a pressure ulcer is considered to be largely preventable with the implementation of an effective preventive strategy,[35] and the occurrence of pressure ulcers has been used as a proxy measurement of quality care. Anaesthetized patients are subjected to prolonged pressure on dependent body parts as neither the position nor duration of surgery can be altered. Duration of surgery is a major risk factor in pressure ulcer formation, in conjunction with the patient's level of tissue tolerance and the support surface. Other risk factors for pressure ulcer formation have been well established (Table 128.9). A constellation of these features is frequently found in the older patient presenting for surgery. On the basis of the literature

Table 128.9 Risk factors for the development of perioperative decubitus ulcers.

Extrinsic
Pressure
Shear
Friction
Moisture
Intrinsic
Age (>40 years)
Nutritional status
Body mass index
Comorbidity
Core temperature
Low diastolic pressure
Low serum albumin
Immobility prior to surgery
Operating room factors
Duration of surgery
Surgical position
Type of mattress
Positioning devices
Warming devices
Epidural anaesthesia/analgesia
Anaesthetic agents
Type of surgery
Extracorporeal circulation
Inappropriate manual handling

to date, prevention of decubitus ulcers in the perioperative period should concentrate on the following points:

- early assessment of risk factors, combined with full history and clinical examination;
- meticulous attention during manual handling, particularly after the patient has been anaesthetized;
- caution during positioning for surgery;
- use of specialized table mattresses such as alternating air devices or gel overlays for patients at particular risk;
- maintaining normothermia;
- maintaining diastolic blood pressure above 35 mmHg;
- low-dose local anaesthetic infusions for regional analgesic techniques;
- frequent re-evaluation.

The role of daycase admission

There is no upper age limit for daycase admission and older patients may benefit cognitively from reduced disruption to their daily environment and routine. Prior consultation at the preoperative assessment clinic should screen patients for suitability. Patients should be medically stable and able to understand simple instructions with regard to medications and fasting. A reminder telephone call the evening before surgery is useful in encouraging compliance. Patients require a responsible companion to accompany them home and to stay overnight. It is this issue that most often causes difficulty. Community services and follow-up need to be in place before the patient leaves the hospital.

Safe sedation of the older patient

Ventilatory responses to hypoxia and hypercarbia are reduced in the geriatric patient with greater risks for apnoea. Changes in volume of distribution, bioavailability and receptor sensitivity lead to alterations in pharmacodynamics for most drugs. Limitations in renal clearance and hepatic function require attenuation of dosage. Since many elderly have prolonged circulation time, longer periods are required for interval dosing. Therefore, titration to effect is an important principle in applying clinical judgment to the geriatric patient. When sedating the geriatric patient, the agent of choice should have a short half-life, with minimal active metabolites and limited side effects. One should avoid using standard dosages calculated on a mg kg^{-1} basis. These boluses frequently produce unwanted respiratory depression and hypotension. Likewise, slower administration of an agent and allowing more time for peak effects often achieve the desired goals with less overall dose.[36]

Choice of surgical approach

The appropriateness of the surgery may need to be reviewed in older patients who, because of their preoperative baseline, are at particular risk of a poor outcome. Unnecessary surgery that exposes the patient to a high risk–low benefit ratio should not be undertaken without expert opinion and full informed consent from the patient. If possible, a less invasive surgical approach may be utilized, for example, thoracoscopic evacuation of haemothorax or laparoscopic-assisted colonic resection. These techniques result in less pain, a quicker recovery and a shorter hospital stay.

Early access to critical care

Although questioned in the past, there are good data in the USA that critical care improves outcome in the elderly and that age should not be used arbitrarily to withhold admission. There are also increasing data which indicate that early, direct ICU admission for some critically ill elderly patients not only prevents a later transfer from the general ward, but also favourably impacts survival.[37]

Perioperative audit

There is an important role for perioperative audit in the care of the older surgical patient. Attendance at preoperative assessment clinics, proportion of patients cancelled for

medical reasons on the morning of surgery, unplanned admission to the ICU, incidence of postoperative myocardial infarction, patient satisfaction and 30 day mortality are just a few examples of outcome measures that may provide scope for audit and implementation of change in individual surgical units.

Conclusion

Good anaesthetic care of the older person involves an assiduous approach to both minor and major elements of the perioperative process. The preparation of the patient begins early and is best carried out in a multidisciplinary unit that is focused on the needs of the elderly. Most information required to plan the anaesthetic may be gained from a detailed history and clinical examination of the patient. Occasionally, special investigations or preparatory procedures are required. Short-acting agents and/or regional anaesthesia are recommended, provided that there are no special indications for general anaesthesia or contraindications to regional techniques. Provision of adequate pain relief with regular assessment and formal charting of pain scores should be adopted as routine practice. Fluid and electrolyte management should not be left to the most junior member of the team – consideration of the fluid, electrolyte and nutritional needs of the patient should be a priority throughout the perioperative course. Oxygen supplementation should be continued routinely to reduce the incidence of hypoxaemia preoperatively and postoperatively.

Key points

- Advanced age is not a barrier to anaesthesia and surgery.
- Anaesthesia should be carried out, or closely supervised, by an anaesthesiologist with sufficient experience of anaesthesia in elderly patients.
- Adequate time must be allocated for a detailed preoperative assessment.
- Invasive monitoring and regional anaesthesia should be utilized liberally.
- Intraoperative anaesthesia care should be viewed as part of a continuum, with therapy such as oxygen supplementation, analgesia and fluid management continued into the postoperative period.

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CHAPTER 129

Health issues in the ageing female

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Cancer

Cancer is one of the leading causes of death in women.[1] The ageing female is at risk for endometrial, ovarian, breast, cervical, vulvar and vaginal cancer. Since there is risk with increasing age, reviewing the risk factors is important to help promote a good quality of life. Proper screening, early detection, treatment and management of comorbidities are essential.

Endometrial cancer

Endometrial cancer is the fourth most common malignancy in women after breast cancer, colorectal and lung cancer. Peak incidence occurs in women between 50 and 60 years of age and the incidence appears to be climbing. The 5 year survival rate for all stages of endometrial cancer has been estimated at 65%.

Risk factors include nulliparity, obesity and prolonged use of unopposed exogenous estrogens. The most common symptom is postmenopausal vaginal bleeding.

Besides a physical examination and Pap smear, a pelvic ultrasonography and either an endometrial biopsy or dilatation and curettage (D & C) is required for diagnosis or exclusion of diagnosis of endometrial cancer. [a positive Papanicolaou (Pap) test for endometrial cancer will only show in 35–50% of the cases and should not be the only determinant in diagnosis.] Optimal treatment is a hysterectomy with bilateral oophorectomy and dissection of retroperitoneal lymph nodes in the pelvic and para-aortic region.[2] Additional treatment, such as chemotherapy, radiation or both, may also be indicated in advanced stages of cancer and discussion is needed with the patient's oncologist and geriatrician to weigh the risks against the benefits.

Ovarian cancer

After endometrial cancer, ovarian cancer is the second most common gynaecological malignancy. Peak incidence occurs in women aged between 50 and 60 years. Risk factors included uninterrupted ovulation (nulliparity or contraceptive usage) and inherited genetic mutations.

Symptoms usually are non-specific. Abdominal pain, abdominal distension and gastrointestinal disturbances are complaints sometimes voiced by women with ovarian cancers, but symptoms may not develop until late in the disease process. Screening, except for high-risk patients, may include ultrasonography and tumour markers; however, it is thought to be of limited value.

Ovaries are generally small and not palpable in postmenopausal women and if upon physical examination an ovary is able to be palpated, immediate evaluation is warranted since it is suggestive of ovarian cancer. Initial treatment involves surgical removal of the tumour. Chemotherapy may be considered depending on the tumour stage, the patient's comorbidities and benefits versus risks. Since most ovarian cancers are detected when the tumour is advanced, long-term prognosis is usually poor.

Breast cancer

Approximately 50% of all new breast cancer cases occur in women over the age of 65 years. The incidence of breast cancer increases up to the age of 80 years, levels out between the ages 80 and 85 years and then is thought to decline. It is difficult to evaluate those over 85 years of age owing to limited data. Risk factors for developing breast cancer may include personal or family history of breast cancer and/or colon or endometrial cancer in the first-degree relatives, nulliparity or late first pregnancy at 31 years of age or older, late menopause, early menarche, abdominal obesity, estrogen replacement therapy and history of atypical hyperplasia on biopsy for benign breast disease.[3]

Screening for breast cancer in a postmenopausal woman includes monthly self-breast examinations, an annual physical examination by a physician or other healthcare provider and a mammogram, yearly or every 2 years. Research has

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shown that screening for breast cancer in women aged 50–70 years has improved survival by early detection. There are many doctor s who feel that mortality could be reduced by 25–30% if all women received proper mammographic screening. There are limited data on breast screening in women over 70 years of age, but it is though that mammography is of benefit. Since 10–20% of all breast cancers are not picked up on mammography, physical examination is also important.

Fewer than 50% of all women aged 65 years or older have ever had a mammogram and those who have obtained one on a routine basis. There has been argument by physicians against instituting routine screening for breast cancer in elderly women, stating that disability and shorter life expectancy may have a direct effect on the desirability and cost-effectiveness of screening. On the other hand, the life expectancy of a healthy woman in her mid- to late-70s is approximately 10 more years and for a healthy woman 85 years of age it is 7 more years. Hence screening appears to be warranted.

The clinical characteristics of breast cancer are the same, despite the age of the individual. Cancer is generally suspected when breast lesions palpated feel firm or abnormalities are detected on mammography. A palpable breast mass in a postmenopausal woman requires immediate attention, since most palpable masses are malignant. All breast masses in this age-group should have a biopsy whether the mass was palpated and/or detected on mammography.

Prognosis is determined by the stage of the disease. Owing to lack of clinical studies, it is unclear whether women over the age of 65 years have the same clinical course as younger women. The course of treatment is prompted by the stage of the disease. Until recently, many elderly women with breast cancer were not aggressively treated; however, today many older women are working with their oncologists and geriatricians discussing various treatment options.

Cervical cancer

Cervical cancer occurs in women of all ages but its incidence peaks in women 40–50 years of age.[4] Symptoms may vary and hinge on the stage of the tumour. Some women may be asymptomatic, whereas others may show clinical signs of postmenopausal or postcoital bleeding. Routine Pap testing is the best method of screening. If the Pap testing is positive, colposcopy-directed biopsies and endocervical curettage are used to establish diagnosis.

Radical hysterectomy is the recommended treatment for cervical cancer. Adjuvant radiation or chemotherapy may also be used. The combined cure rate for cervical cancers is 50–60%.

Vulvar cancer

Vulvar cancer accounts for approximately 3–4% of all gynaecological malignancies in the USA.[5] The average age at diagnosis is 70 years and the incidence increases with age. The most common symptoms exhibited in vulvar cancer are vulvar pruritus, pain and a palpable vulvar lesion; however, many women are asymptomatic.[6] A discharge may be present. Histology generally reveals squamous cell carcinoma. Biopsy may be indicated for diagnosis. Treatment is generally surgical and, for extensive lesions, a radical vulvectomy with unilateral or bilateral inguinal lymphadenectomy is recommended. Radiation and chemotherapy may also be considered adjuvant therapy. Prognosis for early-staged lesions is generally favourable. The 5 year survival rate is 80–90% if there is no metastasis to the lymph node and 16–30% if lymph node metastasis is present.

Vaginal cancer

Vaginal cancer is relatively rare.[7] The average age at diagnosis is 60–65 years. It is estimated that 95% of these lesions are squamous cell carcinomas. Vaginal bleeding or discharge is an early symptom. Pain or post-coital bleeding may be exhibited in sexually active women. Where the tumour involves the anterior vaginal wall, it may cause dysfunction with voiding, since the vaginal wall may invade into the urethra. Biopsy is indicated for diagnosis. Radiation is the main choice of treatment; however, surgery and chemotherapy may be utilized in specific cases. Prognosis is dependent upon the size and location of the tumour. The 5 year survival rate for all types is estimated to be 25–48%.

Menopause

Menopause is the permanent cessation of menses as a result of ovarian ageing. It is clinically diagnosed after 12 months of amenorrhoea. The average age in the USA at which menopause occurs is 51 years. The perimenopausal transition is defined as the time prior to permanent cessation of menses and is identified with irregular menstrual cycles. Transitional time has been shown to vary in length from 2 to 8 years.

Early symptoms of menopause include irregular menstrual cycles, headaches, fatigue, changes in mood and cognition, insomnia and hot flashes (Table 129.1). Some women may experience vertigo, heart palpitations and tachycardia. A later clinical presentation may include urinary incontinence, dry skin, breast changes, genital atrophy with dyspareunia, vaginitis and cystitis.

Early symptoms of menopause are often associated with irregular menstrual periods. They may vary in frequency,

Table 129.1 Signs and symptoms of menopause.

Irregular menstrual cycle
Insomnia
Hot flashes
Mood swings
Cognitive changes
Skin changes
Genitourinary atrophy
Headache
Fatigue
Vertigo
Heart palpitations/tachycardia

duration and blood flow amount. Menstrual bleeding that is unusually heavy, lasting more than 10 days or that occurs more often than once every 3 weeks should be clinically evaluated for possible neoplasms.

Another early symptom of menopause is hot flashes. About 80% of all perimenopausal women report hot flashes and up to 50% of these women may continue to have symptoms for up to 5 years. Hot flashes may also occur after surgical menopause. Research shows that short-term use of hormone replacement therapy (HRT) will help relieve severe vasomotor symptoms, but will not abolish symptoms.

Women who have had bilateral salpingo oophorectomy are at high risk for cardiovascular disease. This is especially true if HRT was not initiated. Early natural menopause is also at high risk.

Diagnosing menopause may be determined by elevated serum levels of follicle-stimulating hormone. Estrogen replacement therapy is the best treatment for symptoms of menopause. Duration of estrogen replacement therapy is controversial and each case should be reviewed for risk versus benefit.

Postmenopausal vaginal bleeding

About 20–30% of postmenopausal vaginal bleeding is due to atypical adenomatous endometrial hyperplasia or endometrial cancer. It may also be caused by the use of estrogens or progesterone or by genital atrophy resulting from low estrogen levels.

History taking should include past and present gynaecological problems. A drug history should indicate whether any exogenous estrogens were used. A pelvic and bimanual examination should be performed to rule out any trauma, tumours or bleeding from atrophic sites. A Pap test should also be performed to aid in diagnosis. Transvaginal ultrasonography may be useful for diagnosis. If the endometrial thickness is less than 5 mm, cancer or endometrial hyperplasia is doubtful. Endometrial thickness over 5 mm is suspicious for malignancy and further work-up is promptly warranted. Endometrial biopsy may then be indicated as well as a full fractional D & C.

If postmenopausal bleeding is found to be cancerous, then treatment should be tumour specific. If cancer is not detected, estrogen treatment is indicated because it may be secondary to atrophy. For those women taking exogenous hormones, the estrogen dosage may need to be decreased and that of progesterone increased. If bleeding continues, a more aggressive work-up is needed.

Postmenopausal hormone replacement therapy

Approximately 6 million women in the USA are taking HRT. The use of estrogen therapy ranges from relief of postmenopausal symptoms to what were assumed, until recently, to be long-term health benefits. Until recently, it was felt that estrogen replacement therapy had a protective effect against cardiovascular disease. From the data collected by the Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II) trial and other recent secondary prevention studies, the new recommendations are against initiating or continuing its use for primary prevention of cardiovascular disease. The Women's Health Initiative (WHI) study stated that estrogen and progestin therapy should not be initiated or continued for the primary prevention of coronary heart disease and it was suggestive that it may stimulate breast cancer growth and hinder breast cancer diagnosis. This condition of hormone replacement also showed an increase in pulmonary embolus.

Sexual dysfunction in the menopausal women

Many women have experienced a lack of interest (decreased libido) or arousal in sexual activity (sexual arousal disorder), achieving orgasm (female orgasmic disorder) or have had pain prior to or during sexual activity (dyspareunia).[8,9] When one or more of these symptoms occur, causing anguish and interference with interpersonal relationships, it is diagnosed as female sexual dysfunction (FSD). The exact prevalence is unknown; however, one survey found that more than 40% of women aged 18–59 years alluded to having sexual dysfunction. It has also been suggested that the prevalence of FSD increases while women are going through the menopause transition.

Peri- and postmenopausal women have repeatedly reported they have lost interest in sex and do not find sex 'pleasurable'. Studies have shown that there has been a decline in sexual functioning from early to late

Table 129.2 Screening questions for female sexual dysfunction.

1	Are you currently involved in a sexual relationship? With men? With women? Both? Multiple partners?
2	How often do you engage in sexual activity? Intercourse? Masturbation?
3	Do you feel that your sex drive has changed? Less? Same? Increased?
4	Do you have difficulty in obtaining an orgasm? Inability? Pain with?
5	Are you satisfied with your current sexual relations?
6	Do you have sexual concerns that you would like to discuss?

perimenopausal. In late perimenopausal to postmenopausal women, studies reveal that there is a decrease in libido and sexual responsitivity, an increase in dyspareunia and a decline in sexual activity. Screening questions that are useful are given in Table 129.2.

The causes of FDS are multifactorial. Hormonal, physical and psychosocial changes are key components of FDS.

Hormonal changes

There is a decline of circulating androgens during the late reproductive years. Androgen deficiency is associated with a decline in libido, arousability and sensitivity to sexual stimulation.

Estrogen deficiency can cause changes in the genitourinary system. Estrogen therapy, both topical and systemic, has been shown to improve vaginal atrophy, increase blood flow to the vagina and increase lubrication.

Physical changes

In addition to the hormonal changes that occur in the genitourinary system, other conditions can contribute to FDS. Limited movement or pain from arthritis may be a factor. Recent pelvic surgery or trauma is another. Some medications, such as antihistamines, antidepressants and blood pressure medication can lead to a decreased libido and inability to achieve orgasm.

Psychosocial changes

A woman may have concerns over the wellbeing of her sexual partner. If she or her sexual partner is ill or have a debilitating disease, it can have a direct impact on sexual function. Women, who live longer than men, are often without a sex partner. Not having a sex partner does not mean that they are no longer in need of nurturing, affection and physical contact. Depression and anxiety can contribute to FDS.

Research has shown that only 14% of Americans aged 40–80 years have been asked by their doctor if they had any sexual problems within the past 3 years. Since this number is relatively small, the physician or healthcare provider needs to remember to inquire about the patient's sexual health along with the history taking during the physical examination.

Data from a large survey have indicated that 68% of men and women thought their physician would be uncomfortable talking about sex and 71% thought that if sexual problems were disclosed, nothing would be done about the problem. Only 14% out of 1384 women ever reported sexual problems to their healthcare provider in a study conducted by the American Association of Retired Persons. Of those women discussing sexual problems, most confer with their gynaecologist rather than their private medical doctor (primary care provider or PCP). It is felt that physicians do not talk about sex because of a lack of education, comfort and confidence and lack of time and treatment options (Table 129.2).

Osteoporosis

Osteoporosis is a major risk factor for fractures in the older population and is estimated to account for approximately 1.5 million low trauma fractures yearly.[10] The lifetime risk of sustaining a fracture to the spine (symptomatic), hip or distal radius in white women is ~40% (but only 13% in white men) aged 50 years and older. The 6 month mortality rate from a hip fracture is ~10–20%. Of the survivors, about 25% will require assistive or nursing home care and ~50% will require an assistive device to aid in their ambulation. Osteoporotic fractures are associated with annual costs in the USA ranging between 7 and 20 billion dollars. About 1–1.5% of all hospital beds in Europe are occupied by patients with osteoporosis. This European figure is expected to more than double in the next 50 years. In the USA, the estimated prevalence of osteoporosis is 8 million in women and 2 million in men and the estimated related health costs exceed 14 million dollars annually. Primary osteoporosis occurs mainly in older people aged 51–75 years and can be arranged in two groups: postmenopausal osteoporosis and age-related bone loss (senescence). The incidence of primary osteoporosis is six times more common in women than in men. Women are at higher risk because they have a lower peak bone mass than men and have an acceleration of bone loss during menopause.

Primary osteoporosis is thought to be atypical in premenopausal women, while secondary osteoporosis composes only a small amount of elderly women. (Elderly women may have a combination of both primary and secondary osteoporosis.)

Age-related bone loss is complex and multifactorial. As one ages, changes occur in the cortex bone, trabecular bone and bone marrow. Studies show that there is a decline in bone mineral density after the third decade of life and it continues to decline at a rate of approximately 0.5% per year. During menopause, women, however, have an accelerated bone mineral density loss at an estimated rate of 3–5%.

Hormonal changes of vitamin D and reduction of calcium absorption also have an impact on ageing bone. Vitamin D levels decrease with age and vitamin D deficiency in elderly people is common. Absorption rates also decline by 40%. Ageing changes in skin reduce the amount of 7-dehydrocholesterol, the precursor and the rate of conversion of vitamin D_3. Declining renal function leads to a decrease in activity of 1-α-hydroxylase, which is responsible for the activation of vitamin D_3. Lower calcium levels then occur from these changes, causing activation of the calcium sensor receptor in the parathyroid gland. Parathyroid hormone is secreted, stimulating osteoclast activity, which keeps serum calcium levels in homeostasis at the price of bone mineralization. Secondary osteoporosis may also have many other conditions causing bone loss such as various endocrine and neoplastic abnormalities, gastrointestinal disease and drug usage (Table 129.3).

Osteoporosis has no symptoms; therefore, a thorough evaluation is critical for detection of osteoporosis. Assessment begins with a complete history alluding to its risk factors as stated in Table 129.4. Major risk factors for osteoporosis are increased age, female gender, ethnicity and thin body habitus. History of previous fracture(s) needs further assessment, focusing on whether the fracture occurred with only minimal trauma (suggestive of low body density). Physical examination for osteoporosis should look for secondary causes. For example, an ill, cachectic woman may need assessment for malnutrition, malignancy or malabsorption syndrome. A loss of body height may indicate vertebral compression fracture(s) or dorsal kyphosis from osteoporosis may be seen on clinical examination.

Table 129.3 Secondary causes of osteoporosis.

Endocrine:
Hyperthyroidism
Cushing's syndrome
Osteomalacia
Paget's disease
Primary hyperparathyroidism
Gastrointestinal:
Malabsorption syndromes
Alcoholism
Neoplastic states:
Bone metastases
Multiple myeloma
Medication:
Anticonvulsants
Excessive thyroid hormone replacement

Table 129.4 Risk factors for osteoporosis.

Advanced age
Female gender
Race (more prevalent among white, Asian and Hispanic descent)
Heredity (~50–80% of peak bone mass is genetically determined)
Small body size/weight (<127 lb/58 kg)
Smoking
Alcoholism
Sedentary lifestyle/immobility
Low dietary calcium/vitamin D intake
History of previous fractures/falls
Decrease long life exposure to estrogen
Certain medication (anticonvulsants, glucocorticoids, thyroid hormone, barbiturates)
Caffeine use
Early menopause or oophorectomy

Laboratory evaluation should reflect clinical findings. All women with osteoporosis should receive a chemistry profile including electrolytes, kidney and liver function, glucose, calcium, phosphorus and albumin. They should also have a complete blood count to rule out anaemia and malignancy. Thyroid function should be assessed in women over 50 years of age. Other laboratory tests should be ordered as individually warranted, such as 25-hydroxy-vitamin D and parathyroid hormone for those with low serum calcium to look for vitamin D deficiency and secondary hyperparathyroidism.

The combination of history taking, physical examination and laboratory tests will help in diagnosing osteoporosis or other secondary causes.

Bone densitometry is the only test which confirms diagnosis of osteoporosis in the absence of fracture. To confirm diagnosis of primary osteoporosis, one needs to rule out secondary osteoporosis, malignancy and osteomalacia. Although many women have some type of knowledge of osteoporosis, healthcare providers need to educate the general population about the importance of taking certain steps to aid in its prevention. Treatment includes providing calcium and vitamin D supplementation, which can reduce the risk of fracture by up to 30%. The best choice in the treatment of osteoporosis is the use of biphosphonates. This group of drugs increase bone mass, thus decreasing the risk for fractures. Other treatment modalities include exercise with a focus on muscle strengthening, weight bearing and balance. Direct effects on bone may be relatively small but will aid in decreasing the incidence of falls which may lead to fractures.

Key points

- Screening for cancer remains important in older women.
- Female sexual dysfunction is a relatively common problem in older women.
- The Women's Health Initiative has decreased the enthusiasm for hormone replacement therapy in older women.
- Osteoporotic fractures are a major cause of disability and mortality in older women.

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CHAPTER 130

Antiageing strategies

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Introduction

The certainty of ageing and death has been a major concern of humans since the beginnings of time, with a consequent never-ending search for methods to combat the consequences of the ageing process and to delay the final moment as long as possible. Current advances in the understanding of the mechanism(s) of the ageing process and the factual extraordinary increase in human life expectancy during the twentieth century worldwide have made it possible to envisage that altering this process and further postponing natural death may actually be plausible in the not too distant future. In addition, not only prolongation of life expectancy is foreseen as the chief aim of research and interventions in the field of gerontology, but also an increase in the number of years without disease and disability, namely, the extension of health expectancy. However, expectations may be higher than what really is scientifically proven. So far, most of the results have been obtained in a wide array of animal models, such as yeasts, worms, flies, mice and primates,[1–4] but the translation of these promising results into humans awaits realistic verification.[5]

Charlatans, swindlers and so-called wise men may take advantage of the incessant wish of people to live longer, proposing miraculous cures and unproven antiageing products that are expensive and very profitable for their proponents but that need to be critically scrutinized. This has led to the concept that antiageing medicine is a fraud and has surrounded the subject with controversy.[6] Conversely, investigators involved in research in the fields of gerontology and geriatrics are making genuine attempts to develop strategies for the prevention and treatment of age-related diseases, functional decline and disability.

The demographic revolution

Human life expectancy increased extraordinarily during the twentieth century worldwide,[7] first because of child mortality reduction and then because of reduced mortality in middle and old age, probably related to medical advances (e.g. antibiotics, vaccinations, improved care of pregnant women, enhanced surgical techniques) and improved socioeconomic conditions during the recovery period after World War II (e.g. improved sanitation, greater food supply, improved work environment and decrease in excessive manual labour). Societal conditions remarkably affect life expectancy, as shown by the rapid increase in life expectancy in East Germany after the fall of the Berlin Wall.[8] Of note, the increase in human life expectancy during the twentieth century took place not only in developed countries, but also in less developed regions, and the pace of the increase was greater in these nations: it is estimated that the over 60-year-old population in China will double in only 27 years.[9] In 1900, 40% of newborns were expected to live beyond age 65 years in developed countries. In contrast, it has been estimated that if the pace of increase in life expectancy over the past century continues through the twenty-first century, most babies born since 2000 in developed countries with long life expectancies will reach 100 years.[10] These dramatic demographic changes will undoubtedly impact societies to a major extent. However, life extension is of little value in the absence of quality of life during the gained years. The imminent rapid increase in numbers of ageing adults will pose major challenges to healthcare systems in the coming years and will have deep consequences for the sustainability of modern society. For instance, the oldest-old group (>85 years), which has been the most rapidly growing segment of the population, is also the most susceptible to disease and disability.[11] Hence now more than ever, the search for ways to prolong health expectancy with effective prevention of disability has become a primary goal in medicine.

The secret to longevity has been related since mediaeval times to a healthy lifestyle and avoidance of excess. As far back as the thirteenth century, Friar Roger Bacon in England stated that in order to live a long life it was necessary to

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follow a controlled diet, proper rest, exercise, moderation in lifestyle, good hygiene and inhaling the breath of a young virgin.[12] The modern equivalent is found in the results of the Norfolk-EPIC study, showing that four simple lifestyle habits (getting some exercise, eating five helpings of fruit and vegetables each day and drinking 1–14 glasses of alcohol per week) were associated with 14 years younger physiological parameters.[13] Another aspect that has been confirmed to be associated with longevity in places such as Japan, Macau and Hong Kong is fatty fish intake, rich in eicosahexanoic and docosahexanoic acids.[14]

Evidence that human ageing can indeed be modified is the fact that disability has decreased in the older population in the USA[15] and Europe.[16] However, recent data suggest that disability rates did not change significantly between 2000 and 2005 among older non-institutionalized Americans.[17] Furthermore, it has recently been suggested that there may be a possible slowing on the pace of life extension observed in the last century because of the poor lifestyle of young people today.[18] The disabled population spends ten times more on care than non-disabled people,[15] hence there are not only important humanitarian but also economic reasons to improve quality of life in old age.

There is currently much promise in research that provides information about the underlying biology of ageing and longevity, which has unveiled possible interventions to slow the ageing process. And a myriad of epidemiological studies have shown that interventions in lifestyle, along with early diagnosis of diseases, appropriate use of advanced medical care and new discoveries that result from basic research may indeed decrease the susceptibility to disease development, increasing longevity and healthspan.

This chapter explores the topic of antiageing therapies from different perspectives. First, it discusses the rationale behind the possible delay of death, disease and disability. Second, some of the advances in biogerontological research in animal models and possible translations into humans are explored. Third, it examines the results of epidemiological studies on lifestyle modification proven to be effective in the promotion of healthy ageing.

What is antiageing medicine?

As far back as the ancients, humans have searched for immortality. Curiously, ancient Egyptians used olive leaves to extend life,[19] while currently there is evidence that virgin olive oil, used as part of the Mediterranean dietary pattern, is associated with longer and healthier lives.[20] Indian ayurvedic medicine has alluded for centuries to 'rejuvenation', developing specific lifestyle rules and herbs to prolong life. One of the most celebrated stories about antiageing is Ponce de León's search for the 'Fountain of Youth' in Bimini, in the Bahamas. Instead, he discovered Florida, where now many American retirees spend their last years in facilities with various amenities and stimulating environments, a true heaven for many elders. The writer James Hilton created in 1933 a place called Shangri-La in his book 'Lost Horizon', which was a paradise where people would not age. Many persons went to search for the fantastic place in the Himalayan Mountains. Even Nobel Prize winners are tempted to believe in magic-bullet remedies for healthy longevity. This is the case of Élie Metchnikoff, who believed that Bulgarians lived extremely long lives due to the use of large amounts of yoghurt in their diets. One of the first books promoting longevity, entitled *Life Extension*, was published by Durk Pearson and Sandy Shaw in 1982. It provided detailed animal experiments and started a long list of self-improvement books that fill the shelves of bookstores worldwide.[6]

Ageing has always been seen as negative since it leads to death. However, now people who have witnessed the recent extraordinary increase in life expectancy want to learn more about what they can do to live longer and healthier lives and to remain vibrant and fit in their later years. As an answer to this widespread ambition, there is a proliferation of antiageing societies, advertisements, products and interventions. The term 'antiageing medicine' was created in 1992 after the foundation of the American Academy of Anti-Ageing Medicine (A4M). Antiageing medicine or interventions are defined by the A4M as 'measures to slow, arrest and reverse phenomena associated with aging and to extend the human lifespan'. It provides a number of certifications in antiageing medicine for physicians, publishes the *International Journal of Anti-Ageing Medicine* and claims hundreds of thousands of members worldwide. Antiageing products have boomed in recent years perhaps due to the ageing of 'baby boomers', who started turning 65 years old around 2010, to the light regulation of antiageing products and easy availability for marketing on the Internet and to the enormous profits that this market can raise. Nevertheless, many of these interventions and products may cause harm, involve economic fraud and may move people away from proved beneficial therapies. Products that claim to reverse ageing mislead the public and impact on the reputation of those doing serious work.

Another example of antiageing initiatives is the Life Extension Foundation, based in Florida and founded by Saul Kent in 1980, which publishes the magazine *Life Extension*, with a readership thought to be ~350 000, and sells dietary supplements by mail order. Two more physicians whose books have promoted antiageing philosophies are Andrew Weil and Deepak Chopra.

Aubrey de Grey, a Cambridge-educated scientist, editor/founder of the journal *Rejuvenation Research* and a regular guest on television programmes, has developed a theory called 'Strategies for Engineered Negligible Senescence' (SENS), which suggests seven types of ageing damage which are readily open to treatment and that

will permit unlimited life extension in the near future: cancer mutations, mitochondrial mutations, intracellular junk, extracellular junk, cell loss, cell senescence and extracellular cross-links.[21] The SENS proposal has been widely criticized by gerontologists, especially because it may make the research community dedicated to ageing studies appear exceptionally optimistic and unrealistic in its promises.[22] Olshansky, Hayflick and Carnes have openly and extensively criticized this approach, stating that 'no currently marketed intervention has yet been proved to slow, stop or reverse human ageing. . . . The entrepreneurs, physicians and other health care practitioners who make these claims are taking advantage of consumers who cannot easily distinguish between the hype and reality of interventions designed to influence the aging process and age-related diseases'.[23]

Numerous concerns about antiageing products have been raised in recent years. One of them entails human growth hormone (HGH), one of the oldest and still most popular antiageing treatments. HGH has been used widely since an article by Rudman *et al*.[24] in the *New England Journal of Medicine* catapulted it to the forefront as a major breakthrough in ageing research in the eyes of the lay public. Several studies on animal models have supported a role for HGH in longevity.[25–28] Nevertheless, a recent meta-analysis showed that the changes in body composition are small and the rate of adverse events is high, including cancer development, weight gain, high blood pressure and diabetes.[29] In addition, studies in mice, flies and nematodes suggest a harmful role.[30,31] Mice genetically modified to produce more HGH live shorter lives than controls,[32,33] whereas mice producing less GH live longer; GH-deficient mice such as Snell mice (pit-1 gene mutation), Ames mice (PROP-1 gene mutation) and Laron mice (GM receptor knockout) live longer than controls. Patients with Laron syndrome (isolated IGF-1 syndrome) have lifespans into their eighties or nineties[34] and receptor mutations in IGF-1, which lead to reduced activity, are more common in centenarians.[35] An extreme example of scam is the HGH nasal preparation advertised and sold on the Internet.

Can death be delayed?

Ageing is a progressive process, universal and irreversible, that takes place at different levels, affecting practically all living organisms, and is the greatest risk factor for death. Ageing and death have been viewed conventionally as programmed events, a kind of immutable biological clock for each individual. However, in several animal models genetic manipulation[25,26] and caloric restriction (CR) without malnutrition[2] have repeatedly been shown to increase the lifespan vs. control littermates fed *ad libitum*, but there is little evidence that this can be translated to humans.[5] On the other hand, numerous studies on dietary patterns[20,36,37] have shown that balanced diets rich in foods of vegetable origin and fish, such as the Mediterranean diet, decrease overall mortality and mortality-associated with cardiovascular disease and cancer, and hence increase longevity. In addition, a high total energy expenditure in 70–80 year olds leads to increased longevity[38] with climbing stairs being the major factor that resulted in an increased total energy expenditure. In fact, there is growing evidence that modifiable lifestyle factors may interact with the ageing process and may alter the susceptibility of an individual to develop age-associated diseases, which are the major causes of mortality.[39] For instance, the best example of healthy ageing is given by exceptionally long-lived persons whose ability to survive appears to be the result of a complex combination of genetics, lifestyle, environmental and psychological factors and chance.[40]

Can the course of disability and functional dependence be reversed?

As age advances, functional capacity reserve decreases and susceptibility to diseases and functional limitations/disability increases. Disability and functional dependence can be reversible to some extent; however, when the functional reserve becomes extremely depleted, the restoration of normal function is no longer possible but the prediction or identification of the 'point of no return' is not yet clear. The development of biotechnological devices, such as the 'exoskeletons' (lifesuits),[41] nanotechnology[42] or bionic implants (e.g. Advanced Bionics cochlear implants),[43] suggests that technology will continue to push that point further away.

Can disability and functional dependence be delayed?

Since the main goal is not only to extend life but also (if not more so) to decrease disability, this is a key question. Indeed, this is the area of geriatrics that has been investigated most intensely, given epidemiological data for a factual decrease in disability in developed countries,[15,16] and the results from numerous studies showing that the onset of disease and disability may in fact be delayed by adopting a healthy lifestyle, by managing chronic conditions such as diabetes and hypertension and by detection and treatment of cancer at an early stage. The recently published INVADE study (intervention project on cerebrovascular diseases and dementia in the district of Ebersberg, Bavaria) demonstrated that moderate to high physical activity is associated with a reduced incidence of cognitive impairment, an important cause of disability, in a large population of older adults.[44] Likewise, the LIFE pilot study found that the rate of onset of mobility disability was lower among a group of older adults who engaged in a structured

exercise programme for 1 year compared with a group of seniors who took part in a health education programme for the same time period.[45] Compression of morbidity and of disability rather than prolongation of survival may be one of the main goals of disease management in the older patient.[46]

Caloric restriction (CR)

Several studies in a wide array of species (e.g. yeasts, worms, flies, mice) have shown that animals under CR without malnutrition have a longer lifespan than control littermates fed *ad libitum*.[1] The first of these studies was published in 1935 by Clive McKay at Cornell University, showing that limiting the food intake of laboratory rats (dietary restriction) resulted in prolongation of their lifespan. Subsequent studies in mice and rats supported the idea that CR delays the ageing process.[2] CR can increase the lifespan of mice by as much as 40% and even greater increases have been reported in non-mammalian models.[3] Recently, striking results from a study in primates were published showing that 50% of *ad libitum*-fed animals survived compared with 80% of CR animals; in addition, CR delayed the onset of age-associated diseases (e.g. cardiovascular disease, diabetes, cancer).[4] However, other studies in monkeys have shown that even if dietary restriction improves metabolic profiles (e.g. glucose, cholesterol)[47] and may attenuate Alzheimer's-like amyloid changes in their brains,[48] these animals also show an increased propensity for bone loss and for the development of hip fractures. In addition, CR fails to extend life in older animals.[33,49] Furthermore, CR does not enhance longevity in all species.[5] Species living in a fairly constant environment will have little opportunity to develop mechanisms to respond to food shortages; this may help to explain why tropical squirrel monkeys respond less to CR than the temperate Rhesus monkey. Also, medflies and some desert-living species (e.g. the spiny mouse) able to depress their metabolism while remaining active in response to food shortage fail to increase lifespan with CR.[5] Several conditions in the laboratory environment may contribute to make the results very variable, even at the same laboratory when studying strains with uncontrolled genetic differences.[50] A recent study found no increase in mean lifespan in wild-derived mice, which had a longer lifespan and lower food intake than the laboratory counterparts. Natural enemies, including pathogens, are greatly reduced in the laboratory and there is a superabundance of food and little opportunity for exercise, which make laboratory animals quite different from animals in the wild and more respondent to CR.[50]

In humans, some studies suggest that CR has a protective effect against atherosclerosis, beneficial effects on cardiac function and some benefits in reducing weight and adiposity,[51] although the benefits were similar to those obtained by exercising. The observation that reducing calories is beneficial to overweight patients is not surprising. A high-calorie diet is unhealthy for most people and a well-known risk factor for the development of atherosclerosis and type 2 diabetes, but the demonstration of a true delay of ageing in humans is not yet viable. Whether CR may also benefit lean people who already have a healthy lifestyle is questionable. Furthermore, CR may have important side effects, such as chronic lack of energy sensation, sexual dysfunction, infertility and mental stress for controlling hungry that may lead to depression and to anorexia.

An organization called the Caloric Restriction Society, founded in 1984 by Ray and Lisa Walford and Brian Delaney, have members who observe CR to varying degrees. Studies in this group, funded by the Nutritional Institutes of Health, have shown that the middle-aged among the members have lower blood pressure, glucose and cholesterol values[52]. However, multiple studies have shown that weight loss increases mortality, institutionalization and hip fractures in persons over 60 years of age.[53] Hence CR may be harmful in elders who are at particular risk of malnutrition.[54]

There are currently several CR-type diets advertised to the public as a method of prolonging life. The CRON diet (Caloric Restriction with Optimal Nutrition), developed by the founders of the above-mentioned society, recommends a 20% CR based on individual basal metabolic rate. The Okinawa diet, a low-calorie, nutrient-rich diet, is founded on the original diet of people living on the Japanese island of Okinawa (Ryuku Islands), which has the highest concentration of centenarians in the world. The diet has fewer calories than a traditional Japanese diet and consists mainly of vegetables (especially sweet potatoes), a half serving of fish per day, legumes and soy. It is low in meat, eggs and dairy products. Other diets based on similar food combinations, such as the New Longevity Diet, have been developed. None of these diets have been proven to extend longevity and Roy Walford, a major proponent of dietary restriction, died at 79 years of age of amyotrophic lateral sclerosis (ALS). Of note, animal studies have suggested that CR is especially hazardous for animals with ALS.

Numerous mechanisms have been proposed to explain why CR may promote longevity. One of these mechanisms is autophagy or cellular self-digestion, involved in protein and organelle degradation. A common characteristic of ageing cells is the accumulation of damaged proteins and organelles that predispose the cells to a pathogenic phenotype with aggregate-prone mutant proteins. These deposits of altered components are particularly detrimental in non-dividing differentiated cells, such as neurons and cardiomyocytes, where the age-dependent functional decline usually manifests. It is proposed that the decreased autophagy with age may play a major role in functional deterioration. CR seems to improve autophagy induction,

possibly owing to lower levels of insulin, an autophagy inhibitor.[55] Another mechanism proposed to explain CR effects is hormesis, which states that CR represents a low-level stress that allows the animal to develop enhanced defences and to slow the ageing process.[56] It has also been suggested that CR reduces oxidative damage, enhances insulin sensitivity and decreases tissue glycation.[57]

CR mimetics

Current efforts aim to reproduce or mimic the beneficial effect of CR, without its side effects. Interest is particularly high with regard to CR mimetics as possible therapies for obesity. Autophagy induction has been tested through the use of antilipolytic drugs, which mimic the starvation state induced by CR.[55] Another CR mimetic, which upregulates autophagy, is rapamycin (sirolimus) or its analogue everolimus.[58] It has recently been demonstrated that treatment with this antibiotic delays ageing and extends lifespan in yeast,[59] *Caenorhabditis elegans*[60] and mice.[61] The 'silent information regulator' (Sir) gene is upregulated by CR in yeast and in mammals and sirtuin-activating compounds (STACs) are under development. Resveratrol, an antioxidant component in red wine, is a STAC that has been shown to extend lifespan in yeast, flies and worms[62,63] and to modulate insulin secretion and action.[64] Although it is possible that resveratrol is healthy, just as other antioxidants contained in vegetables and fruits, or may have a positive effect on the prevention of age-related diseases such as diabetes, there is at present no evidence that it can delay, even slightly, the human ageing process.

Epigenetics

This is a field that has recently been linked to longevity. Epigenetics refers to changes in gene expression caused by mechanisms other than changes in the underlying DNA. These changes may remain through cell divisions for the remainder of the cell's life and may also be transferred to the next generation. For example, nutrition might induce epigenetic changes that could be transmitted to the next generation, impacting on health. It has been shown that the ancestors' food availability and nutrition during the slow growth period before the prepuberal peak is followed by different transgenerational responses, which are the main influence on longevity.[65]

Translation of results into humans

Can the results of biogerontological research in experimental models be extended to humans? This is an unresolved question. There have been attempts to search for similarities in the IGF-1/insulin signalling (one of the main regulators implicated in the ageing process) in *C. elegans* and humans.[66] A 6.4-fold increase in lifespan in *C. elegans* was first reported secondary to a single base mutation in daf-2, the equivalent of IGF-1 receptor in humans,[67] but the relationship between insulin signalling and ageing seems to be more complicated in mammals: insulin-receptor knockout mice die in early neonatal life of diabetic ketoacidosis.[68]

Even though genetically modified animals such as dwarf mice have shown extreme lifespans[25,26] and rats bred to have high aerobic capacity had fewer cardiovascular risk factors than control rats,[69] the identification of genetic determinants of human longevity is still inconclusive. Although many plausible candidate genes have been proposed, only one finding [apolipoprotein E (Apo-E)] has so far been replicated.[66] The initial expectation that a few rate-limiting targets modulate ageing has been contrasted with the finding that over 100 gene manipulations may increase longevity in *C. elegans*.[66] Another important downside in the search for longevity determinants is that mortality trends seem to be stochastic in nematodes[70] and in humans,[66] with enormous variations in lifespan.

Stem cell ageing

It has been proposed that age-related defects in stem cells can limit proper tissue maintenance and contribute to a shortened lifespan.[71] In competitive repopulation experiments, there was little difference in haematopoietic stem cell (HSC) activity 4 weeks after transplantation in young versus old HSCs. However, at 8 and 16 weeks post-transplantation, old HSCs showed a reduced contribution compared with young control HSCs.[71]

It has been suggested that stem cell ageing may determine the ageing process, but the connections at different levels are complex. At the genomic level, both internal and environmental factors may cause alterations in individual or groups of genes through epigenetic changes with direct damage to DNA. However, it is not clear whether age-related epigenetic changes render DNA more susceptible to damage or DNA damage underlies epigenetic changes.[72]

The emergence of possible therapies with stem cells in order to regenerate tissues, for example the heart, has created a fair amount of hope. However, the response to stem cell therapies has been shown to be different in aged as compared with younger animals. In an animal model of induced myocardial infarction, cardiac structure and function were reversed dramatically in young animals treated with granulocyte colony-stimulating factor and stem cell factor, but old animals did not show any benefit.[73] On the other hand, stem cells with a muscle-specific IGF reversed the muscle loss (sarcopenia) seen in ageing mice[74] and a major predictor of disability.[75] A recent review of the possible role of stem cell ageing as a determinant of human ageing concluded that a more precise mechanistic understanding is needed before it can be translated into human

antiageing therapies. The authors recommend adhesion to a healthy lifestyle (smoking cessation, a balanced diet and regular exercise) as the most clinically validated advice at the moment.[76]

Nevertheless, the colossal advances in stem cell research in the past few years cannot be ignored. Induced pluripotent stem (iPS) cells created from skin cells first in mice[77] and then in humans[78] and the induction of insulin secretion in iPS mouse cells[79] may open paths for future potential therapeutic possibilities, provided that they prove to be safe.

The hormonal fountain of youth

Towards the end of the nineteenth century, Brown-Séquard suggested that a testicular extract produced remarkable antiageing effects. The powerful effect of placebo was demonstrated, since it is unlikely that his extract had any testosterone. Many wealthy men in Europe and the USA received monkey testicular implants and claimed that they had rejuvenation effects. Brinkley in the USA pioneered the use of 'goat gland' extracts, which were equally ineffective, but made him a rich man. Subsequently, almost every hormone has been publicized as having antiageing effects. The case of HGH, with many rich persons paying exorbitant amounts of money to attain everlasting youth, has already been mentioned. Dehydroepiandrosterone (DHEA) is similarly promoted for antiageing therapy. Despite positive animal studies,[80] well-controlled human studies have failed to show any beneficial effects.[81,82] DHEA replacement showed to increase bone mineral density in a randomized controlled trial, but the effect was relatively small compared with traditional osteoporosis therapies.[83] Likewise, 2 years of DHEA supplementation did not change body composition, muscle strength, insulin sensitivity or quality of life. DHEA may improve some metabolic parameters and measures of psychological wellness in subjects with adrenal insufficiency, but the benefit is not consistently sustained in long-term therapy.[84]

Of the hormones, the best available positive data are for vitamin D. A meta-analysis showed that vitamin D replacement decreases mortality,[85] improves function, decreases falls and prevents hip fracture in persons with 25-hydroxy-vitamin D levels below 30 ng ml^{-1}.[86] There is agreement about the need for older persons either to get regular skin exposure (15–30 min per day) without sun block or to take 800–1000 IU of vitamin D per day. All persons over 70 years of age should have their 25-hydroxy-vitamin D levels measured at least yearly (preferably in winter) and, when needed, have their level raised above 30 ng ml^{-1}.

Similarly to HGH, testosterone levels decline with ageing (in both men and women). Some, but not all, studies have shown that low testosterone is associated with increased mortality in males, but the findings are confounded by the decrease in testosterone levels induced by illness.[87–92] Meta-analyses have shown that testosterone improves sexual function and muscle mass and strength in older men.[93,94] Bone mineral density in hypogonadal men increases under testosterone substitution.[95] However, fracture data are not available, hence the long-term benefit of testosterone warrants further investigation. In oophorectomized women, testosterone enhances sexual function.[96] This has led to the development of selective androgen receptor molecules, which appear to improve power in older males and females.[97] The role of testosterone in older persons is established for the treatment of sexual dysfunction (both low libido and in some cases erectile problems).[98] A recent consensus statement from diverse international scientific societies has provided valuable guidelines for the diagnosis of age-associated testosterone deficiency syndrome, for treatment with testosterone supplementation and for the identification of possible adverse effects and contraindications of such treatment.[99] A careful selection of candidates, an appropriate dosing of hormonal supplementation and an attentive clinical follow-up are crucial instruments for the correct use of testosterone replacement therapy.

Even though short-term estrogen/progesterone replacement therapy (HRT) to treat severe menopause-related symptoms and to reduce osteoporotic fracture risk in selected postmenopausal women is well established, its long-term use for disease prevention has generated extensive debate. Studies conducted in the USA[100,101] and the UK[102,103] showed no effect on protection against cardiovascular disease and even suggested that this therapy may increase the risk. Recent reanalysis of these trial results supports positive cardiovascular outcomes provided that HRT is initiated within 10 years since menopause. The favourable benefit–risk ratio for HRT decreases with ageing and with time since menopause.[104] Moreover, HRT seems to increase the incidence of dementia when initiated in women aged 65 years and older.[104] Hence current guidelines recommend HRT use close to menopause, when indicated, for the shortest time and at the lowest dose possible.

Anabolic steroids are emerging as possible candidates for adjuvant therapy during rehabilitation, and it is possible that they will play a role in improving healthspan. However, their potential harmful prostatic effects[105] suggest that they possibly will not be used as longevity agents.

Studies by Morley and co-workers in mice have shown that pregnenolone is a potent memory enhancer.[80] Nevertheless, results in humans have been largely negative, hence at present pregnenolone should not be used as a memory enhancer or an antiageing hormone.[106]

The hormone melatonin, produced by the pineal gland, also declines with ageing. Although it has antioxidant properties and has hypnotic effects, overall it appears to have minimal effects as an antiageing agent.

Most of data available for antiageing interventions relate to hormonal replacement treatments. However, despite initial promising results in the past decades, currently available data do not validate an extensive use of hormones in order to reverse or delay the ageing process, with the exception of vitamin D. Despite these facts, many unscrupulous charlatans prescribe and probably will continue to prescribe and supply hormones inappropriately and ageing people will continue to use them avidly with the dream of eternal youth. In reality, the search for a hormonal fountain of youth has been as disappointing as Ponce de León's search for a fountain of youth.

Preventive gerontology

Ageing is by far the main risk factor for a wide range of clinical conditions that are at present the most frequent causes of morbidity and mortality. It is now widely accepted that ageing is the result of the sum of damage during the course of life, with consequent alterations in several functions of the organism that may favour the development of diseases commonly observed in old age. One of the most accepted mechanisms, among over 300, to explain the ageing process is the excessive mitochondrial production of free oxygen radicals [reactive oxygen species (ROS)] – called oxidative stress – with damage to cellular structure and subsequent inflammation.[107,108] Oxidative stress accumulates when pro-oxidants overwhelm the antioxidant defence mechanisms and has been implicated in diverse age-associated chronic diseases, including atherosclerosis, cardio- and cerebrovascular disease, cardiometabolic syndrome, obesity, type 2 diabetes, osteoporosis and osteoarthritis, neurodegeneration (Alzheimer's disease, Parkinson's disease), cancer, depression, sarcopenia and frailty.[109,110] ROS serve as precursors to the formation of oxidized low-density lipoprotein (LDL), essential to the formation of atherosclerotic plaques.[110] Elevated ROS have also been associated with an increased expression of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, plasminogen activator inhibitor (PAI)-1 and interleukin (IL)-6.[111] Chronic inflammation has been associated with a broad spectrum of degenerative diseases of ageing, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and age-related macular degeneration, and has been also proposed as one of the main causes of frailty in older persons.[112] This concept has led researchers to seek factors that may reduce or contrast the cellular damage or enhance the repair mechanisms, hence delaying the beginning of diseases and improving the quality of life in older age.

Antioxidants

It is now widely accepted that consumption of fruits and vegetables, natural products that are rich in antioxidants, appear to prevent multiple diseases. However, there is no evidence that persons taking vitamin supplements have a longer life than those who do not take supplements. Studies on vitamin E and cardiovascular disease in humans have found that supplementation either has no effect or is harmful.[113] Similarly, studies of the effects of vitamin E on cancer have shown mixed results. Vitamin E had minimal effects on persons with Alzheimer's disease.

The ATBC trial demonstrated that β-carotene supplementation was associated with an increased incidence of lung, prostate and stomach cancer.[114] The CARET study also resulted in an increase in lung cancer mortality in persons previously exposed to asbestos who received β-carotene preparations.[115] No effects with β-carotene supplementation have been also demonstrated for cardiovascular disease in a number of studies.[116] Similarly, vitamin C has been shown to have minimal beneficial effects. α-Lipoic acid, a powerful antioxidant, has been proved to be useful in the treatment of diabetic neuropathy.[117] It reversed memory disturbances in SAMP8 mice, a partial model of Alzheimer's disease,[118] but it seemed to increase mortality rate in mice. A recent Cochrane review concluded that multivitamin/mineral supplements conferred no benefit in preventing cardiovascular disease.[119] In summary, human studies do not support the use of antioxidant vitamin supplementation.

Lifestyle

Numerous epidemiological studies have shown that interventions in lifestyle (e.g. smoking cessation, a balanced diet, regular physical and mental activity) may decrease the susceptibility to disease development, increasing longevity and healthspan. A healthy lifestyle has demonstrated positive effects on longevity also in older populations. As mentioned, centenarians have generally adhered to a healthy lifestyle. A prospective study conducted in 2357 men showed that modifiable biological and lifestyle factors, assessed at a mean age of 72 years, were associated with exceptional longevity of 90 or more years and with high functional status in late life.[120] The EPIC-Norfolk study showed that not smoking, getting some exercise, eating five helpings of fruit and vegetables each day and drinking 1–14 glasses of alcohol per week[13] provided an estimated 14 year improvement in chronological age. Thus, encouraging favourable lifestyle behaviours, including smoking abstinence, weight management, blood pressure control and exercise, may not only enhance life expectancy but may also reduce morbidity and functional decline in later years.

Exercise

A growing body of evidence has accumulated in the past two decades confirming that promotion of physical activity

is perhaps the most effective prescription that physicians can formulate to promote ageing successfully. Practically all age-related diseases leading to physical disability during late life are linked in some way to a sedentary lifestyle. Indeed, exercise in moderation appears to be a cornerstone of longevity. Mice with an excess of phosphoenolpyruvate carboxykinase (PEPCK-C) in their skeletal muscle are more active than their controls and can run for 5 km at a speed of 20 m min^{-1} compared with 0.2 km for control mice.[121] These mice live longer than controls and females remain reproductively active until 35 months of age.

Observational studies in humans have strongly suggested that those who are physically active live longer. It has been shown that high total energy expenditure in 70–80 year olds leads to increased longevity,[38] with climbing stairs being the major factor that resulted in increased total energy expenditure. Fries found that older runners had 13 years delay in the development of disability compared with a group of sedentary older persons.[122] Likewise, the LIFE-Pilot study demonstrated that a structured physical activity programme significantly improved functional performance, measured with the Short Physical Performance Battery, which includes walking, balance and chair stands tests, and the 400 m walking speed, suggesting that this type of intervention may offer benefit on more distal health outcomes, such as mobility disability.[45] Walking speed is associated with decreased disability and physical activity is associated with decreased dysphoria. Persons aged 50 years of age who exercise regularly are less likely to develop Alzheimer's disease as they age.[123] In addition, it has been reported that regular physical activity reduces the rate of deterioration in persons with dementia.[124]

Diet

A myriad of studies have shown that different components of a balanced diet may contribute to decrease the incidence of cardiovascular disease, diabetes mellitus and some types of cancer. There is mounting evidence that a dietary pattern similar to that followed by traditional populations living in the Mediterranean basin during the post-World War II period, based on bread, grains, olive oil, legumes, fruits, fresh vegetables, nuts and fish, has remarkable effects in reducing total mortality, cardiovascular mortality and cancer-related mortality.[16,36,37,125–134] The Mediterranean diet includes a significantly large amount of plant foods rich in antioxidant compounds, which may help to explain its multiple benefits. A study conducted in 74 607 subjects without coronary artery disease, stroke or cancer at enrolment recruited from 10 European countries concluded that every 2 unit increment in a score constructed with the above-mentioned elements of the Mediterranean diet conferred a reduction of 8% in overall mortality.[36] In patients with coronary heart disease at baseline, the reduction in overall mortality was even higher, with a 27% reduction in mortality.[37] The Mediterranean diet has also been demonstrated to decrease the incidence of diabetes mellitus in different populations[135,136] and to decrease the need for hypoglycaemic therapy for newly diagnosed diabetics.[137] A recent meta-analysis of 12 large studies including a total of over 1.5 million subjects confirmed a significant reduction in all-cause mortality associated to increases in Mediterranean diet score adherence.[20] The meta-analysis also included recent studies demonstrating a reduction in the risk of developing Parkinson's[138] and Alzheimer's[139] disease. Also, the incidence of depression has been shown to decrease with increased adherence to this dietary pattern.[140] All the studies on the Mediterranean diet emphasize the effects of the whole dietary pattern with the combination of different nutrient-rich and antioxidant foods rather than individual elements. In fact, the effects of the combination of components of a balanced diet may potentiate the effect of single elements, as shown by the effects of a 'polymeal' on cardiovascular events frequency. Analyses of data from the Framingham heart study and the Framingham offspring study showed that combining different foods with well-known evidence of cardioprotection (wine, fish, dark chocolate, fruits, vegetables, garlic and almonds) would reduce cardiovascular events by 76%.[141]

Ethical issues

Antiageing medicines raise a number of ethical issues. For instance, in a society with limited resources, is extending the life of older populations appropriate? How would one approach the question of life extension if it is associated with cognitive impairment? Is extending life duration without improvement in quality appropriate? Will it be possible for most people? How long is it appropriate to extend life for: 5, 10, 50 years, . . ., or is it appropriate to think about a future life extension of 100 years? There are no simple answers to these questions and certainly they belong not only to scientific and philosophical areas, but also to ethics, fiscal regulations and religious beliefs.

Another concern is the use of technological advances. Technology may make our life better, but the price paid sometimes is high and a world that depends completely on technology may be a world of slaves. It is essential that well-controlled human trials are carried out so that we do not end up shortening rather than prolonging lifespan. In addition, technological advances may not be available for the majority of people, which may generate rising discrimination and inequality issues.

What should be considered as successful ageing? The measures for successful ageing entail physiological parameters such as disease incidence, mobility and mental acuity, but also important psychological determinants, including resilience, emotional wellbeing, connectedness and

spirituality. In fact, psychological factors such as sociality, conflict avoidance and adaptiveness seem to be associated with exceptional longevity,[142] and resilience, or the ability to cope with adversity and losses, has been associated with healthy longevity.[143] With respect to older patients, the multidimensional aspects are even broader and may include, for instance, having autonomy over the place and manner of the final days.[144] With these concepts in mind, it is possible that the achievement of disease/disability avoidance and life extension may have less value if other determinants of wellbeing are not taken into account.

Conclusion

Who does not hope for longevity combined with good health in later years? However, since ageing is so complex, it is unlikely that one pill or a single magic bullet procedure can slow the ageing process. In recent decades, striking advances in the understanding of the ageing process have come from studies of animal models, but the translation of positive results to humans is not yet realistic. Therapies that are highly effective in animals can be highly toxic in humans. Even if simple solutions that may require some physical labour are not easy to put in practice, a balanced diet of moderate proportions, in addition to regular exercise, today remains the best clinically validated advice, namely, the only proven fountain of youth.

Demographic changes will mould new contexts of societies and of developments around the world and will test the capacity of health systems to provide quality of life for millions of older persons. Support systems from governments and social agencies will be needed to cope with the tough challenges of these new societies that should focus on the promotion of healthy ageing. The factual prolongation of the 'active life expectancy' of the population in past decades suggests that disease and disability may indeed be delayed. Compression of morbidity and of disability rather than prolongation of survival may be one of the main goals of disease management in the older patient.

The geriatrician may play an important role in educating older persons about the positive and negative faces of antiageing strategies. It cannot be ignored that in the future stems cells, information/communication technology, nanotechnology and robotics will change the practice of medicine. The potential for these strategies, such as stem cells to rejuvenate diverse tissues, cochlear implants and retinal computer chips, is enormous, but their application to humans is only just starting.

Continuous advances in medical knowledge contribute to increased longevity and improved quality of life. Even taking into consideration the possible negative sides, medical advances are at present the strongest antiageing medicine. However, the ageing public continues to spend billions of dollars on antiageing remedies of unproven value. Geriatricians have an essential role as educators on how to age successfully.

Key points

- Interventions in lifestyle (e.g. a diet rich in fruit and vegetables, low in saturated fats, salt and sweetened drinks, without *trans*-fatty acids; regular moderate exercise; smoking cessation; drinking 1–2 glasses of alcohol daily; fish consumption) decrease the susceptibility to age-associated disease development and mortality, and hence delay ageing.
- Animal studies reporting interventions that increase longevity are often assumed to be directly applicable to humans before appropriate clinical trials have been performed.
- There is no evidence that hormones, vitamins or antioxidant supplementation prolong life.
- Vitamin D replacement, in persons with low 25-hydroxy-vitamin D levels, decreases hip fractures, decreases fall incidence, improves muscle strength, enhances function and decreases mortality.
- Antiageing medicine has been taken over by swindlers who promote unproven, potentially dangerous and expensive remedies to a credulous ageing public.

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CHAPTER 131

Ethics in geriatric medicine

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Scenes from everyday life in the Geriatrics Unit, or how do you do what's right?

A selection of scenes (case histories)

Mrs A

Mrs A, 90 years old, is admitted after a fall. She lives at home alone, but was able to call for help thanks to her remote alarm device. This is the third time in six months that she has been admitted for a fall. No particular cause could be identified, apart from moderate balance disorders.

Mrs A has two sons, one is a surgeon and the other a lawyer. Naturally worried about their mother, they refused to let her return home and raised the idea of nursing home placement. They said that if she was allowed to go home, they would hold the physician responsible for the accident that, in their view, would inevitably ensue.

Mrs A does not see things in the same light. A former militant in the women's lib movement, with a strong character, she decidedly wants to go home. She also has mild cognitive decline, some memory difficulties that she denies and a Mini Mental State Examination (MMSE) score of 24/30. What should you do?

Mr B

Mr B is 75 years old, a former metallurgy worker, with polyvascular disease and several risk factors (former smoker, hypercholesterolaemia). He had a heart attack three years previously, followed by a variety of complications. He now has a pacemaker for permanent systolic pacing. He has stage IV lower limb arteriopathy, with early-stage necrosis of the right toe. After a consultation in vascular surgery, Mr B accepted to undergo transmetatarsal amputation, which was scheduled rapidly. He was supported and encouraged in this decision by his family. However, the day before the scheduled operation, he suffered a left sylvian stroke with hemiplegia and aphasia.

What is the right decision? Should the operation go ahead? What should you do?

Mr C

Mr C is 81 years old, a former gymnast, physical education teacher and amateur opera singer. He suffers from severe dementia. He had just moved to a new nursing home, after his family suspected some elder abuse in the previous one. He has considerable behavioural problems and every evening at nightfall he gets agitated and shouts, with the shouting increasing in intensity if he is locked in his room. He tends to roam and wanders into the other residents' rooms, making them afraid of him. The families of other residents are complaining about him. The manager of the nursing home asks the doctor to give Mr C something to calm him. What should you do?

Mr D

Mr D is aged 85 years, a former marketing director, and up to now had been enjoying an active retirement, dividing his time between his grandchildren, his activities in various associations and some travelling. He was found lying on the ground in his house, 3 h after a fall from which he was unable to get up. In the Emergency Department, the cause of the fall was found to be a silent infarction with probable paroxysmal cardiac arrhythmia. The cardiac care unit refused to take him on the grounds that they only had one bed free, which 'had to be reserved' for a potentially younger patient. In the end, he was admitted to the geriatrics unit and the cardiac threat passed, but he developed acute renal insufficiency due to 'crush syndrome' brought on by the fall. The nephrology intensive care unit is reluctant to take him for haemodialysis because of his advanced age and the cardiac risk.

Should the physician insist? What should you do?

The approach to ethical debate

The above four situations clearly introduce an ethical debate: how do you do what is right?

General ethical reflection based on moral philosophy filters down into these situations, where decisions are

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difficult because there is a conflict of values. Morals, law and ethics are intimately related. Moral philosophy tries to define universally what is right, what is good and what is evil through imperatives, and tries to act fairly. The law fixes rules, duties and limits for life in society. Heteronomous law applies to everyone from the outside and in a formal manner. Ethics is a process of questioning, in special situations, with a view to doing what is right for others and what is good in general and making fair and efficacious decisions. It could be defined as 'philosophical wisdom that guides practical existence towards the representation of good' in specific situations. Through the questions that it raises, medical ethics seeks to determine what is right, taking into account the state of scientific knowledge and also the constraints related to the patients and their psychological, social and economic environment.

There are no ethics specific to advanced age. Conversely, in elderly populations, there are particular situations that call for increased ethical vigilance.

The primary ethical principle, around which all the others are based, is the principle of humanity and dignity. From birth to the grave, every person belongs to a community of human beings and, as such, possesses a unique quality that cannot be estimated, measured or compared. As stated by Kant, dignity is essential, superior at all costs and can stand neither equivalent nor quantification, comparison nor commerce.

These reflections on general ethics have particularly concrete applications in ethics as applied to healthcare. For example, a patient with advanced Alzheimer's disease, bedridden and mute, has no less value or dignity than the physician caring for him or than the politician shaping the laws governing the management of this patient's dependence.

Similarly, very elderly persons are citizens in their own right, who can and should be able to state their opinion. These persons have stood the test of time and, in many cases, possess a wisdom that merits respect. Their rights and duties should by no means be rescinded (except in special clinical circumstances).

However, it is obvious that although the principles are straightforward, their application in daily life is often problematic: on the one hand, because of the attitude of our society towards elderly people – our productivist society exalts youth and decries old age, which incites fear – and, on the other hand, because of the frailty and vulnerability of many elderly people, often also compounded by cognitive decline that can alter their judgement.

Obstacles and restraints

The obstacles and restraints that prevent us from having an ethical attitude towards elderly people are manifold. It is useful to distinguish between obstacles that arise from the organization of the healthcare system and health professionals' behaviour and those that arise from the frailty of the patients themselves. The former are manifested by 'ageism', which is reflected by forms of exclusion based solely on age. This form of exclusion is all the more hypocritical since it is rarely labelled as such.

Restrictions on access according to age are the most visible form of this phenomenon, such as limited access to prevention, refused access to certain diagnostic or therapeutic techniques or even refused access to certain hospital units. While it is important that there be a thorough reflection on the risk–benefit ratio, frailty and prognosis when justifying the use of therapy that can often be highly invasive, it is nonetheless unacceptable that age alone be a justification for excluding fully independent elderly people.

On the other hand, many medications are prescribed in elderly people. They may appear to be useful, but their efficacy is often unproven. The side effects can be numerous, but poorly documented, since frail elderly patients are excluded from most randomized clinical trials that are the basis for approval of drugs for release on to the market.

This situation therefore calls for vigilance and citizenly commitment to the ethics of responsibility on the part of all health professionals (physicians, nurses, nurses' aids, administrators, etc.). As Emmanuel Levinas reminds us, the human part of man is his responsibility for others. The physician cannot simply diagnose, treat or prognosticate, but must take a stand on behalf of the patient, all the more so when this vulnerable and elderly person has trusted him.

Lack of competence or negligence by health professionals constitutes a further obstacle to an ethical attitude. This is particularly true in the field of geriatric medicine, where scientific knowledge and management practices are rapidly evolving.

One of the primary ethical requirements for health professionals is the duty to update their knowledge regularly, to maintain an acceptable level of competence.

Let us consider a few examples:

- Nowadays, how can we imagine telling an elderly person who is complaining of moderate memory problems that 'it's only natural, it's your age', without proposing appropriate assessment of cognitive function? Especially when there is a risk that, a few months or years later, the patient will be diagnosed with Alzheimer's disease that could have been detected much earlier?
- How is it possible that, according to some studies, almost half of the cases of Alzheimer's disease will never be diagnosed, including (and especially) when the disease causes the patient to be placed in a nursing home?
- How we can explain the frequency of iatrogenic disease, which often reaches dramatic proportions in these polypathological patients? Iatrogenic diseases could

often be avoided if the physicians had been sufficiently knowledgeable about drug–drug interactions and the specific modalities of prescription in frail elderly patients.

• How many dependent, elderly patients, through lack of information, do not receive the material or financial aid that they require?

Hence among situations where there is an ethical dilemma regarding elderly persons, we must distinguish between the ethical risk that comes from the outside (societal views, institutional constraints, economic pressures, attitude of health professionals and/or their level of competence, etc.) and the risk that is related to the patient themselves.

Fit elderly persons who have aged successfully should be treated in the same manner as their younger counterparts. Fit elderly persons make up a considerable proportion of the population, but since they rarely make use of health-care services, they are never really the topic of much discussion.

Conversely, a sizeable proportion of the elderly population is characterized by its frailty and vulnerability. The exhaustion of the physical reserves required to deal with perturbations and stress, and also frequent polypathologies, quickly draw these subjects into a downward spiral.

The presence of cognitive decline with alteration of judgement further complicates the decision-making process, in which many of these subjects are no longer able to participate. Instruments for reflection, as proposed by Renée Sebag-Lanoë and later Jean-Marie Gomas, become indispensable in these situations, where it is important to adopt an ethical approach.

When the situation is complex and ambiguous, the best solution is not always immediately obvious. An ethical debate should then be initiated. According to the fundamental principles of humanity and dignity, Childress and Beauchamps, in the earliest days of bioethics, proposed four principles (without any particular hierarchy), namely autonomy, beneficence, non-maleficence and, finally, justice and equality. We might also add the principle of solidarity.

These principles are moral values that have been formulated explicitly, but numerous other moral values come into consideration and competition implicitly when there is an ethical debate, such as freedom, truth, privacy, honesty, integrity, respect, security, fraternity, protection of the weak, and so on. There is no hierarchy, either formal or explicit, between these values. Each person will implicitly create their own hierarchy of values, based on their history, their experience in life, their philosophical concepts, their religious beliefs or their professional and/or institutional position. Indeed, the choice of the values to prioritize could even change depending on the context or the person's relation with the patient. This personalization of the criteria serves to enhance the utility of ethical debate, where there are no 'good guys' or 'bad guys', since no one is either right or wrong. Institutional conflicts, conflicts of interest, family conflicts or economic pressures also often compound the complexity of the debate.

The 10-point approach

In this context, it is important to distinguish the moral values at stake on the one hand and the underlying conflicts on the other, as there are no 'ready-made' solutions. A 10-point approach can be proposed and requires multidisciplinary consultation.

'The patient is a person'

The most important point is to restore the patient to their status as a 'vulnerable person' and restore their humanity. This implies listening to the patient, looking at them, asking their opinion, which is of vital importance (according to the tenets of the so-called 'Kouchner' law of 4 March 2002), asking the patient what they understand about their situation and what their wishes are.

Even a person in cognitive decline can express their wishes, if the available alternatives are proposed in a simple fashion.

The conflict of values

Subsequently, the situation can be examined from an ethical point of view, that is, every effort must be made to identify the moral values at stake and consider all the possible outcomes.

Collect additional information

• What is this patient's main disease? (Incomplete diagnosis? Stage of evolution? Prognosis? Any open therapeutic options? Iatrogenia?).

• Does the patient suffer from any other diseases and, if so, how are they interlinked with the primary disease? Possibility of a downward spiral? Prognosis?

• Know your patient: what do they know about their disease, what are their desires to live, fight, cooperate, consent to care? What does their body language express? Are they suffering (note the utility of visual analogue scales and, for non-communicative patients, non-verbal scales such as Doloplus, Algoplus and EPCA).

• What do we know about the patient's environment? Living conditions? Family circle or extra-familial circle? Personal relationships? Mode of relations? Desires? What can be learned from the patient's previous decisions in their personal relations or from their life story?

The family

The family has to be taken into consideration. Do they regularly come to visit the patient? Did someone meet the family to inform them about the patient's situation? What do they think of the situation? All these points must be taken into account, albeit without placing the burden of decision on the family.

Initiate debate within the team

Initiating the debate implies finding the time to bring together all the members of the caregiving team and those who take care of the patient on a daily basis, in order to give their opinion about how they see the situation and what they know of the patient. Confronting all these points of view can often be very informative.

Often, it is also necessary to include outside experts in the debate, to acquire a wider range of viewpoints. Such outside contributors could include a psychologist or the palliative care team when end-of-life situations are being considered. If there is enough time, an Ethics Committee could also be asked for advice.

Identify the ethical risks

- Lack of knowledge regarding the disease, the patient, the family, and so on.
- Difficulty controlling fantasies and projections, particularly in end-of-life situations.
- Lack of multidisciplinary consultation.
- Failure to take into consideration the patient's family and environment.

Take sufficient time

Real emergency situations are few and far between. Generally, the emergencies are more of a psychological nature. Taking sufficient time to reflect provides an opportunity to step back, escape the pressure and analyse and reflect appropriately.

There are more solutions than problems

The team discussions and multidisciplinary consultations in the previous steps should produce a range of proposed solutions. A certain amount of imagination is required. A single solution is often the wrong one. A two-sided solution is often restrictive. Finding three or even four alternatives gives the impression that a real choice is available.

Naturally, it is then necessary to assess the feasibility, acceptability, legal suitability and potential cost of each proposed solution, in order to establish a hierarchy among the possibilities. The final choice will often be made in the end by trying to find the best balance between beneficence (doing the most good, often including the most risky solution) and non-maleficence (doing the least harm, including the least risky solution).

Take responsibility for the decision and explain the choice

Someone has to make the final decision and take responsibility for it. This is the role of the physician caring for the patient (general practitioner or hospital physician). Although the discussion must be open, the decision cannot be collective. Once a final decision has been made, the physician should make sure that the patient consents to the proposed solution and then explain the modalities of implementation to the family.

Take notes and re-evaluate

Every decision must be clearly documented and notified in the patient's medical file and be signed by the physician who made the decision, with mention of all the people who participated in the decision-making process. This documentation can be used as a reference. In this file, it should always be specified at what time point in the future this decision should be reviewed, in order to ensure that the decisions remain appropriate even when the patient's situation has evolved.

Conclusion

The main aim of this reflection on the ethics related to frail, elderly patients is to maintain or restore the patient's basic dignity as a human being. It also reminds caregivers of the fundamental values that underlie their profession, based on respect and solidarity for all, and can give their work new meaning thanks to the changes brought about by this new ethical vision.

Key points

- Morals, law and ethics are intimately related.
- Decisions that are expected to be taken by doctors are often difficult because there may be a conflict of values.
- The application of medical ethics is intended to seek to determine what is right, taking into account the state of scientific knowledge and also the constraints related to the patients and their psychological, social and economic environment.
- This situation therefore calls for vigilance and citizenly commitment to the ethics of responsibility on the part of all health professionals.

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CHAPTER 132

Participation of older people in clinical trials

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Introduction

The need for clinical trials involving older people

The ageing of the global population has brought about a greater need to understand the health status, underlying risk factors and prevention and care needs of older people.[1] Observational epidemiological studies on ageing, such as the Baltimore Longitudinal Study on Aging, Women's Health and Aging Study, Health Aging and Body Composition Study, Rotterdam Study and PAQUID, are now well established and have shown that the recruitment and retention of older adults in clinical studies are clearly feasible.

The most reliable evidence regarding the efficacy of interventions aimed at preventing, curing or managing a disease or health status comes from randomized controlled trials. However, traditionally, older people have been excluded from such studies,[2] meaning that the level of participation in clinical trials is highly disproportionate to the level of health burden, healthcare expenditure and prescription drug use in this population.[3] For example, in cancer trials, only around one-third of participants are thought to be elderly, whereas over 60% of incident cancers occur in elderly persons.[4,5] Older adults are even under-represented in trials for diseases that almost exclusively affect older people, such as osteoarthritis[6] and dementia.[7] Aside from the evident need to test treatments for specific age-related diseases, such as dementia, age-related macular degeneration, osteoporosis or cataracts, in elderly populations, another important reason for conducting clinical trials on older people is that in this population drug doses may need to be adapted to physiological changes associated with old age in order to avoid serious adverse events, and also the high level of comorbidities and concomitant medications must be taken into account.

Why are older people excluded from clinical trials?

There are various potential reasons for the exclusion of elderly people from clinical trials, for example, patient fear and misunderstanding of research, physician bias against suggesting enrolment in trials (perhaps through fear that elderly people will not be able to withstand aggressive therapies) or too rigorous exclusion criteria that eliminate many potential participants.[8,9] Although age in itself is not now generally used as an exclusion criterion, older people may be excluded from trials on the basis of haematological, hepatic, renal or cardiac abnormalities that may be widespread in this population. Furthermore, trial participants may be required to be ambulatory, to be able to walk and to be able to carry out activities of daily living independently, thus excluding further categories of older people. The use of strict inclusion and exclusion criteria for clinical trials is favoured by researchers since it ensures a more homogeneous study population, which may facilitate demonstration of efficacy. However, trials based on such populations provide little indication of real-life effectiveness.

Even if the inclusion and exclusion criteria allow their participation, investigators may be deterred from enrolling older subjects due the numerous methodological difficulties of conducting research with older people, for example, high rates of dropout or death, selection bias and the presence of comorbidities and multiple medicines (polypharmacy). Rates of attrition (or 'dropout') are higher in trials carried out in older populations than those carried out in younger individuals,[10] which reduces the statistical power of trials to detect treatment effects and can affect the validity of the results obtained. High attrition rates can be brought about in trials of older adults due to death, worsening health, decreasing autonomy, institutionalization and refusal to continue trial participation, often because of the perceived burden of study visits. Also, trials for older people often require the participation of another family member or close friend, at the very least in order to transport or accompany the participant to study visits, but in some cases to act as a proxy in order to give information about the patient's health status and/or quality of life if the patient is incapable of giving this information him- or herself. This may impact on attrition bias, since if the family member cannot or does

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not want to participate, then the participant will have to withdraw from the study. There may also be problems with the validity of using information gained from proxies since one cannot be sure that it is a valid or reliable measure of the patient's actual health status. A further problem in trials of older people is selection bias, since older individuals who participate in research studies are generally healthier than those in the general population. Finally, elderly people are likely to have a high rate of comorbidities and risk factors for various diseases, which bring about risks of drug interactions, side effects, death and hospital admission, all of which may be seen as having negative influences on trial findings.

Consequences of the exclusion of older adults from clinical trials

The exclusion of older people from clinical trials limits the generalizability of their findings, since there will be insufficient data about positive or negative effects of treatment in this specific population, which may well contain individuals with the greatest need for new treatments.[5] This can result in suboptimal treatment for older people – either through not receiving potentially useful therapies because of a lack of evidence or through exposure to unnecessary risks because of a lack of information on adverse events in older people of therapies tested in trials involving primarily younger subjects.[11]

There are therefore now calls for trial participants to be more representative of the patient population for the disease under study;[12] for many chronic diseases, this will require the inclusion of significantly more older people. Despite the methodological complexities highlighted above, it has been demonstrated that clinical trials can be successfully carried out both in healthy older subjects[13] and also in those with serious illnesses.[14] Furthermore, it has been shown that older people are willing to participate in clinical trials.[11]

Given the projected increases in the number of older adults in the coming years, there is an urgent need to develop new interventions for the prevention, treatment or management of age-related syndromes and diseases. It is therefore important to increase the participation of older adults in clinical trials.

Summary of existing clinical trials involving older people

Clinical trials reported in the literature

A search was carried out in the PubMed database in order to quantify the number of clinical trials for older people reported in the literature since 1990. The total number of articles per year indexed in the database and classed as randomized controlled trials has tripled in the last two decades, gradually increasing each year from ~6700 papers in 1990 to ~18 000 papers per year in 2007–2009 (Figure 132.1). The proportion of these trials conducted specifically in older populations has also increased over time from ~3% per year in the 1990s to ~5% per year since 2003 (Figure 132.2).

Clinical trials recorded in an online registry

Another source of information about clinical trials is the online clinical trials registry ClinicalTrials.gov. A search in August 2010 showed that there were 266 intervention trials specifically for 'seniors' registered in the database. These studies represented 0.4% of the total number of registered intervention trials.

The earliest registered trial that was specifically for seniors began in 1990, but there were only two such trials prior to 1997. Between 1998 and 2002, there were between 4 and 10 trials per year for seniors and since 2003 there have been more than 20 trials per year (Figure 132.3). Since 1997, these trials have generally represented less than 0.5% of all intervention trials per year (Figure 132.3).

Of the 266 seniors trials identified, 156 were ongoing or not yet started as of August 2010 (recruitment status: 'Recruiting'; 'Enrolling by invitation'; 'Active, not recruiting'; or 'Not yet recruiting'). Most of these trials were focused on a specific condition such as cancer ($N = 63$) or cardiovascular disease ($N = 20$), whereas others were targeted towards more general syndromes of ageing, such as frailty and sarcopenia ($N = 12$) or 'healthy ageing' or the prevention of disability ($N = 4$) (Figure 132.4).

Most of these trials for seniors are taking place in Europe ($N = 93$) and North America ($N = 56$), with other regions clearly under-represented, participating in at most 12 trials (Figure 132.5). Africa is the least represented region in clinical trials for seniors and is only participating in one trial at the present time.

Determinants of participation of older people in clinical trials

The factors that motivate older adults to participate in clinical trials may differ from those that motivate younger individuals. The specific identification of barriers and motivators that prevent or facilitate the enrolment of older adults in clinical trials, and also factors that are predictive of enrolment, can inform the development of strategies aimed at increasing the participation of this population of individuals in future trials.

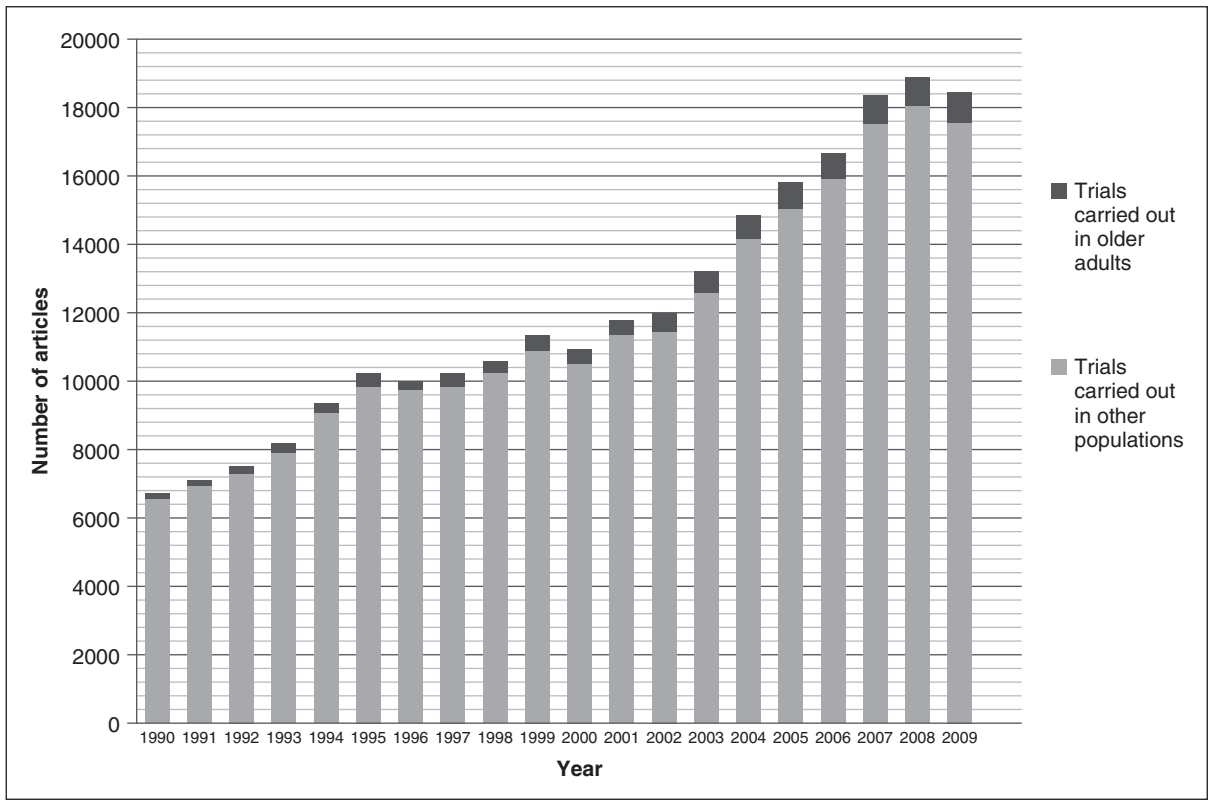

Figure 132.1 Number of articles indexed in PubMed reporting randomized controlled trials, by year of publication.

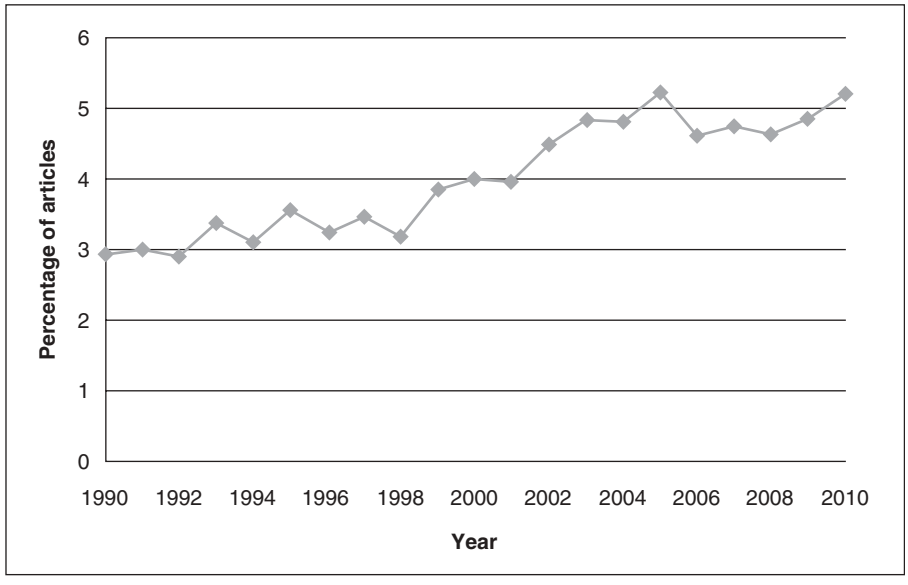

Figure 132.2 Percentage of articles indexed in PubMed reporting randomized controlled trials carried out specifically in older subjects, by year of publication. Results for 2010 do not include the whole year (search carried out in August 2010).

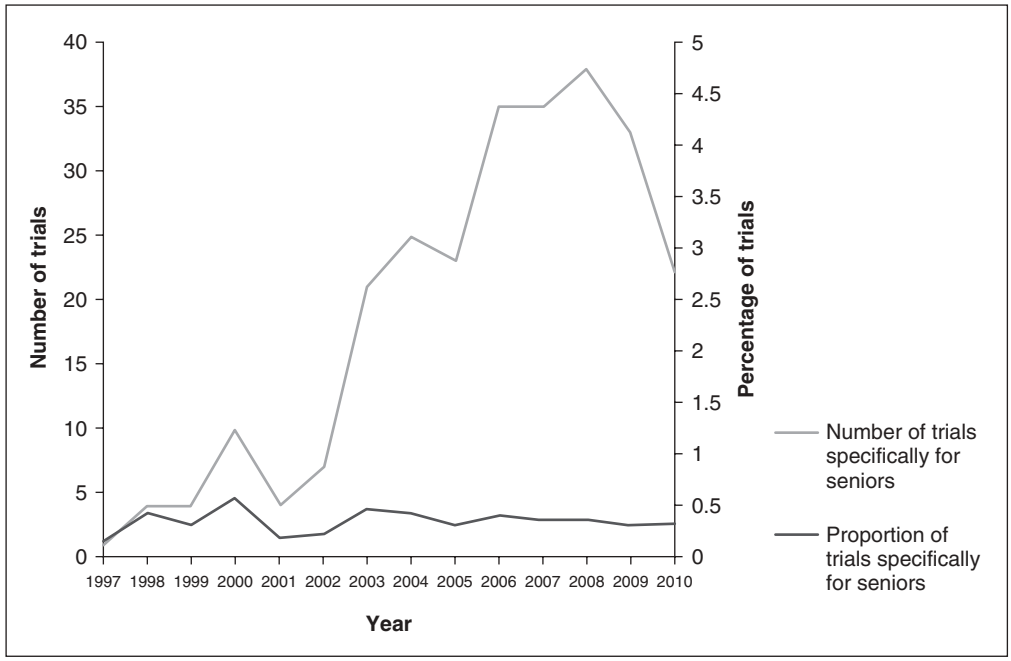

Figure 132.3 Number (grey line) and percentage (black line) of intervention trials specifically for seniors registered in the ClinicalTrials.gov database, by trial start year. Results for 2010 do not include the whole year (search carried out in August 2010).

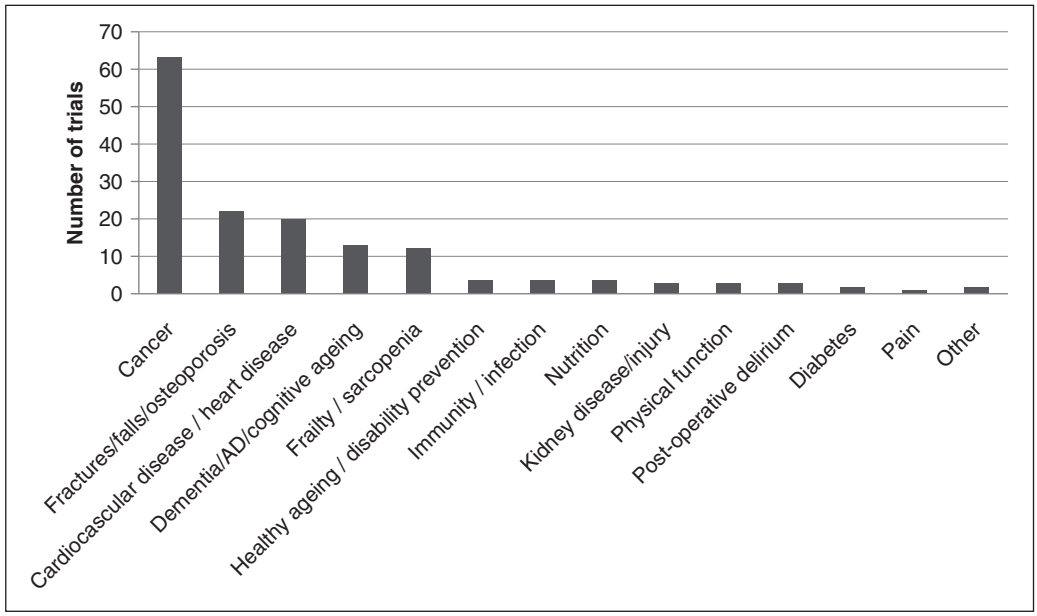

Figure 132.4 Primary conditions targeted by the 156 ongoing clinical trials specifically for seniors registered in the ClinicalTrials.gov database.

Patient factors

Patient factors associated with participation or non-participation

There are few studies that have made a detailed comparison of the characteristics of older people who enrol in clinical trials with those who do not enrol, perhaps due to the ethical difficulties of obtaining detailed information from non-participants. Other studies have assessed factors associated with willingness to participate in a clinical trial, often in a hypothetical situation, rather than actually comparing those who do and do not participate in an actual trial.

Sociodemographic factors

Whereas some studies have found no difference in terms of demographic characteristics between older adults participating in certain trials and those not participating,[15,16] others have suggested that age and level of education or socioeconomic status can affect older adults' participation in clinical trials. A review of the literature noted that older people with a lower level of education or lower socioeconomic status are less likely to want to participate in research or actually do so.[11] Indeed, non-participants in a lifestyle intervention trial for patients with stable cardiovascular disease had a lower level of education than participants,[17] as did non-participants in an intervention study on successful ageing for people aged 65 years compared with participants in this study.[18]

Even for clinical trials specifically targeting older adults, age seems to be predictive of trial participation. For example, in a primary prevention trial for Alzheimer's disease for people aged 75 years or older, persons under age 85 years were more likely to enrol than those aged over 85 years.[19] Also, participants in an intervention study on successful ageing for people aged 65 years or more were younger than non-participants[18] and non-participants in a lifestyle intervention trial for patients with stable cardiovascular disease were older than participants.[17]

There is little information regarding gender differences between participants and non-participants in clinical trials for older adults, although it was noted that men were more likely to enrol than women in a primary prevention trial for Alzheimer's disease.[19]

Disease severity and general health status

There is little information regarding the relationship between disease severity and trial participation in older adults.

General health status may affect older adults' participation in clinical trial since it was found that participants in an intervention study on successful ageing had better physical status and functional abilities and fewer depressive symptoms than non-participants.[18] Another study showed that while eligible refusers and participants (from the usual care control group only) in a disability prevention trial in older adults were similar in terms of self-perceived health at baseline, refusers had a significantly higher rate of mortality [adjusted relative risk (RR) 1.49; 95% confidence interval (CI) 1.15–1.93; $p = 0.002$] during 3 years of follow-up.[16]

Other factors

Other factors that may be associated with trial participation amongst older adults include prior experience or knowledge of clinical trials,[11] the person giving the informed consent for participation (the patient him/herself or a proxy if the patient is incapable of giving their own consent) and marital and working status. For example, patients themselves were more likely to accept to participate in an acute stroke trial than proxies (if the patient was incapable of giving informed consent)[15] and non-participants in a lifestyle intervention trial for patients with stable cardiovascular disease were more likely to be single and less likely to be working, compared with participants.[17]

Patient-related motivators for participation

As a complement to the identification of patient characteristics associated with participation in clinical trials, some studies have attempted to determine the reasons driving older adults' participation in clinical trials.

Personal benefit

The potential for personal benefit is clearly a strong motivator for the participation of older adults in clinical trials. Personal gain (feeling better or living longer due to the treatment) was amongst the most frequent reasons likely to influence the willingness of older cancer patients to participate in clinical trials,[20] and personal health benefits were the most common motivation for postmenopausal women to participate in a cardiovascular trial.[21] Similarly, for older women with breast cancer, the most common reasons for participating in a trial were that it would provide access to the best treatment available and bring about an improvement in their health.[22]

The reasons rated most highly for participation in a cardiovascular lifestyle intervention trial were having poor health and willingness to change lifestyle to improve health,[17] indicating a desire for personal benefit through taking part in the trial.

Interest in research

An interest in or desire to support research also seems to be a common reason for older adults to participate in clinical trials. For example, participants in a trial of statins for older adults with vascular disease or risk factors most commonly stated that curiosity/interest in the study and wanting to support research were the factors motivating them to respond to an initial invitation letter about the study.[23] Also, more than 40% of postmenopausal women who indicated

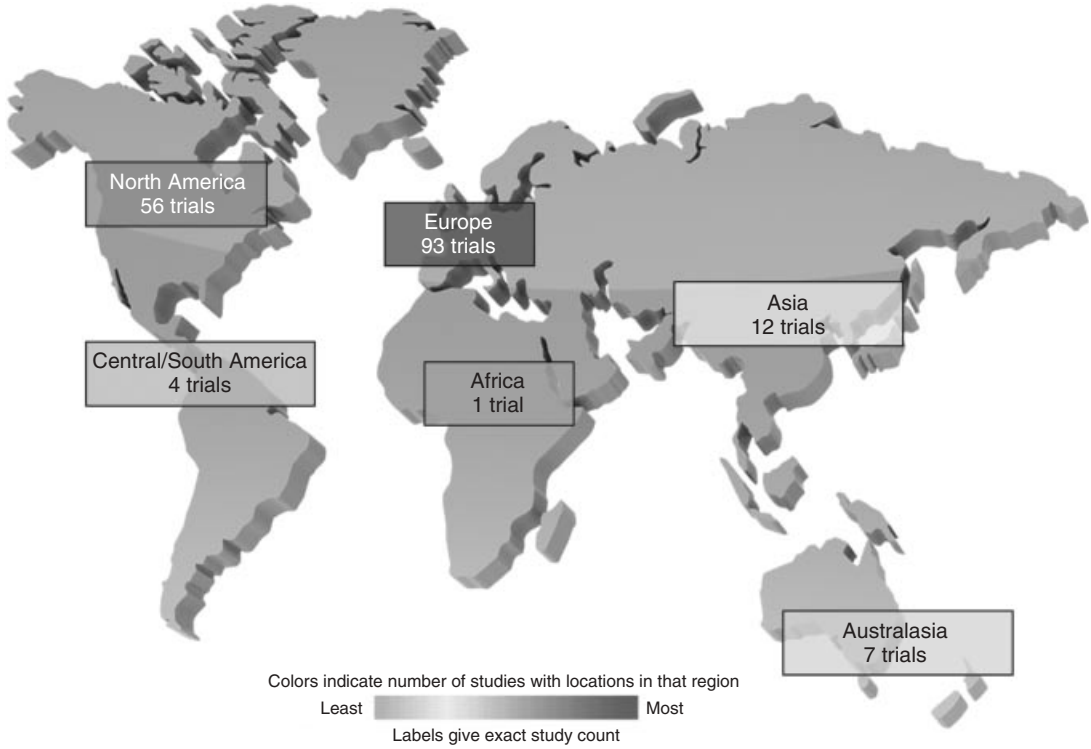

Figure 132.5 Participation by region in ongoing clinical trials specifically for seniors registered in the ClinicalTrials.gov database.

that they would participate in a cardiovascular clinical trial stated that an interest in research was one of their motivations.[21]

Altruism

A desire to help others and to give something back to the healthcare system is also a common motivator for participation in clinical trials. The possibility of benefiting society was given as a motivation to participate in a cardiovascular trial by around one-third of postmenopausal women who indicated that they would participate in clinical research,[21] and for older people taking part in a nutrition trial the most important reasons reported for taking part in the trial were helping the research team and medical knowledge and helping other older people.[24]

Patient-related barriers to participation

Finally, the determination of older adults' reasons for not participating in clinical trials can help to identify the barriers preventing the broader inclusion of this population in clinical trials.

Financial costs/time investment

The financial costs associated with participation and the time investment required are important barriers to the participation of older adults in clinical trials; these were the main barriers reported by non-participants in a cardiovascular disease lifestyle intervention trial.[17]

Lack of interest in research/negative perceptions

A lack of interest in the trial was the primary reason for refusal to participate in a prevention trial for Alzheimer's disease involving people aged 75 years and older.[23] Reluctance to participate in a research project was also the primary reason for non-participation in a randomized controlled trial of influenza vaccination in fit, healthy individuals aged 65–74 years.[25]

Poor self-perceived health

Poor health seems to be a common reason for older adults not to participate in clinical trials, especially for primary or secondary prevention trials. For example, self-perceived poor health was the second most common reason for refusal to participate in a primary prevention trial for Alzheimer's disease,[19] and personal illness was the most common reason given by postmenopausal women for not participating in a cardiovascular clinical trial.[21] About 15% of respondents in this study were also reluctant to increase their medication intake.

Comment

A number of patient-related factors have therefore been identified which seem to facilitate or prevent the

participation of older adults in clinical trials. It is interesting to note that one study[16] showed that refusers may be a relatively heterogeneous group of people who refuse participation for different reasons, which could explain the differences between studies in terms of the characteristics of refusers and trial participants. The authors identified four separate groups of adults aged 75 years and older who had refused to take part in a disability prevention trial: those who did not participate because they considered themselves 'too healthy', those who thought they were 'too ill', those who had 'no interest' in taking part and those with 'other' reasons for not taking part, with relatively different baseline characteristics.[16] The medical and demographic characteristics of refusers were associated with their reason for refusal. For example, those who had refused because they were 'too healthy' ($N = 105/401$ refusers) had better perceived health, were less likely to receive home-help care and were less likely to have seen a physician during the 6 months prior to baseline compared with trial participants. On the other hand, those who refused because they were 'too ill' ($N = 51$) were older, had poorer self-perceived health, were more likely to received home-help care and more likely to have seen a physician during the 6 months prior to baseline than participants. Also, overall, refusers were found to have a higher rate of mortality than trial participants during 3 years of follow-up after the study inclusion, but a subgroup analysis showed that in fact it was only the 'too ill' and the 'no interest' subgroups that had a higher risk.[16]

Furthermore, different factors may be related to participation at different stages of the recruitment process for clinical trials (e.g. initial contact, presence at screening visits, uptake of intervention).[26] The nature of the trial and its intervention is also likely to be important and there may be differences between older people who accept to take part in primary prevention trials and those who take part in a treatment trial for a specific disease. The nature of the disease (e.g. life-threatening or not, disease burden, chronicity) and the nature of the intervention (e.g. lifestyle intervention versus pharmacological treatment, high-risk versus low-risk surgery) are also likely to play important roles. Indeed, a study of patients with primary and secondary colorectal cancer showed that patients with different stages of the same disease had very different fears and anticipations of drug trials (e.g. patients in the secondary stages of the disease were more motivated by altruism, whereas patients in primary stages were more motivated by personal benefits).[27]

Physician factors

In addition to factors related to older adults themselves, physician-related factors also can also play a role in the participation of older adults in clinical trials.

Physicians can play a major role in determining whether or not older adults will participate in a clinical trial. For example, recommendations from a cancer doctor for or against participation were the highest ranked reasons for older cancer patients' decisions to participate or not in a clinical trial.[20] Also, in the same study, a recommendation from the family doctor was more important for trial participation than recommendations from family or friends.

Older adults may have greater confidence in physicians involved in their everyday care than physicians carrying out research studies: nearly one-third of healthy older individuals questioned about their reasons for not participating in a trial of influenza vaccination stated that they would prefer their own doctor to give the vaccine.[25]

Effect of patient characteristics

In addition to giving their opinions about trial participation, another aspect of physicians' roles in determining the participation of older adults in clinical trials is their attitude and preferences towards 'offering' clinical trial options to individuals.[28] However, there has been relatively little research into this subject. One study showed that breast cancer patients aged 65 years or older were less likely to be offered trial participation than younger patients in one study.[22] Also, a study of the willingness of primary care providers to encourage enrolment of hypothetical patients into cancer prevention trials showed that geographic location, younger vignette patient age (65 versus 80 years) and higher trust score were significantly and independently predictive of primary care providers recommending trial enrollment.[29] Factors that were not associated were: existing breast cancer chemoprevention trials, knowledge of the outcome of a different trial testing the same drug, experience of using the study drug and perceived changes to control in patient care.

Barriers to the participation of older adults in clinical trials, according to physicians

Physicians' opinions about the barriers to the participation of older adults in clinical trials can help us to understand why they may not bring up the subject of clinical trial with certain patients. A review[30] of physician-perceived barriers to the inclusion of older adults in cancer trials highlighted the following factors: comorbid conditions and toxicity of the treatment; lack of support for the older patient to manage side effects at home; patient preference and influence of their families; transportation needs; patient difficulty in understanding the trial; excessive time required to enrol older patients; lack of coverage for certain healthcare costs related to clinical trial participation; physicians' personal bias that one arm of the trial was not effective or unacceptable; perceptions that the best treatments for their patients were not included in the trial; that the life expectancy of

some patients was too short to justify participation in clinical trials; or that the likelihood of success was low in many trials. Significant barriers to Alzheimer's disease clinical trial referral also included physician concerns about exposure of patients to uncomfortable tests and procedures and a lack of time to discuss research participation.[31]

Physician characteristics and knowledge

Certain physician characteristics, such as specialty, age, gender and percentage of patients older than 65 years, may not be associated with their likelihood of offering clinical trial participation to older patients,[22,31] although physicians who were more likely to refer patients to Alzheimer's disease clinical trials saw greater benefits to patients, families and their practice compared with physicians who were less likely to refer.[31]

A further reason for physicians not discussing trial participation with their patients is that they may not be aware that a trial is available.[30] A study of factors affecting primary care providers' referral of patients with cancer to clinical treatment trials showed that attendance by the primary care provider at clinical trial educational sessions was a consistent predictor of referral.[32] Close proximity to a specialist Alzheimer's Disease Research Centre was the strongest predictor of referral by community physicians of patients to a clinical trial for Alzheimer's disease,[31] perhaps because physicians working closer to specialist research centres are more aware of ongoing trials than other community physicians.

Environmental/logistical factors

Finally, environmental or logistical factors, including characteristics of the trial, may affect the participation of older adults in clinical trials.

Transportation and distance to the study centre

Transportation can be a major barrier to participation in clinical trials for many elderly people,[11] either through reduced physical mobility or inability to continue driving. Transportation issues were cited as a reason for non-participation in a cardiovascular trial by nearly one in five of the postmenopausal women who declined to participate in the trial.[21] It is also unsurprising that the distance to the research institution can also play a major role in determining older adults' participation in clinical trials.[11] Non-participants in a cardiovascular disease lifestyle intervention trial, for example, cited distance to the study centre as an important reason for non-participation (even though on average they lived the same distance from study centres as trial participants).[17]

Incentives/cost

Although older people do not rate material gain highly as a reason for participating in research,[11] and may therefore be less susceptible to incentives than younger participants, they may be unwilling to support additional costs for taking part in a trial, such as transportation costs and healthcare insurance (in some countries). Indeed, costs were amongst the main barriers reported by non-participants in a cardiovascular disease lifestyle intervention trial.[17] Revision of the US Medicare system in 2000 allowed coverage of trial visit costs, but it is unclear if this has affected the number of older adults participating in clinical trials.[11]

Trial characteristics

There has been little study of the effect of trial characteristics in relation to the participation of older adults. Research has mainly been focused on the risk of the intervention and potential side effects. For example, participation in an acute stroke trial was inversely related to the risk of the proposed trial intervention.[15] In trials of pharmacological interventions, the risk of side effects is clearly an important factor. Postmenopausal women invited to take part in a cardiovascular trial gave concern about adverse health effects as one of their reasons for not participating,[21] and older adults approached to take part in an influenza vaccine trial were also concerned about side effects.[25]

Communication

One-quarter of people questioned about their reasons for not participating in a trial of influenza vaccination in healthy older individuals stated that they objected to the term 'geriatric medicine' on the letter of invitation,[25] suggesting that the way in which trials are presented to older adults, including the language used, is also an important influence on participation. A lack of interest in clinical trials could be driven by negative media stories about medical research abuses or concerns about commercially driven motives for trials.[23]

Facilitating the access of older people to clinical trials

The review of patient, physician and environmental factors associated with the participation of older adults in clinical trials shows that there are numerous modifiable barriers which could be targeted. In order to demonstrate the evidence of strategies aiming to remove such barriers, randomized controlled trials are needed, but so far very few have tested the efficacy of an intervention aimed at increasing the participation of older adults in clinical trials.

Table 132.1 Other proposed strategies.

Theme	Strategy
Exclusion criteria	Relaxation of exclusion criteria affecting older adults: • Avoidance of upper age limit • Use of medical exclusion criteria only when justified Sensitization of ethics committees to the problem of unjustified exclusion of older people from clinical trials

Primary healthcare providers' awareness of clinical trials	Neither primary healthcare providers nor older patients may be actively seeking clinical trials:
	• Inform and educate clinicians and primary healthcare providers about the existence of clinical trials for ageing and age-related diseases
	  • Educational seminars and materials for physicians
	  • Development and promotion of clinical trial registries
	  • Encourage physicians to discuss clinical trial participation with eligible patients

Recruitment strategies	Tailor recruitment strategies for older people: • Mass media may not be appropriate for trials for specific conditions • Face-to-face contact is important for older adults • Telephone contact may also be useful, but may not be suitable in all instances, e.g. for older adults with hearing problems • Other recruitment methods should be investigated, such as home visits and referrals by primary healthcare providers
Presentation of clinical trials to potential participants	Sufficient time must be set aside to explain clinical trials to older adults and for their decision-making process: • Older adults may not be familiar with the concept of clinical trials, so the general aim of clinical trials should be explained (with a clear explanation of issues such as randomization or blinding) • The details of specific trials should be clearly explained, including the risks and benefits • Written materials should be tailored towards older adults, bearing in mind that some may have a relatively low level of education. Prejudicial language such as 'geriatric' or 'elderly' should be avoided • If physicians themselves do not have enough time to discuss trial participation with their patients, other personnel should be made available for this purpose • Family members should be included in enrolment discussions if possible (even if a repeat visit is required) • Material should be provided with information about the trial relative to carers and family members who may help in the decision-making process for older adults • Give sufficient time for older adults to discuss participation with their families and close friends
Participant costs (time and financial)	Personal costs (both time and money) should be minimized. Transport problems should be addressed: • Free transport (such as a minibus or taxi) could be provided to bring participants to the study centre • Travel costs could be reimbursed • Family members or friends who drive participants to trial visits should be thanked • Home visits could be offered as an alternative, although they may not be acceptable to all participants The burden of study visits should also be kept to a minimum: • Avoid redundant or unnecessary evaluations
Maintaining communication	• It is important to maintain good communication between participants and trial staff throughout the study • Consultation with older people can improve recruitment strategies and overcome barriers to participation for future trials • Feedback of the results of a trial could provide an opportunity to interact with the older adults and may encourage them to participate in future trials Trial researchers should also engage with clinicians who work with older adults on a daily basis in order to inform the design and implementation of research involving older people

Strategies tested in randomized controlled trials

Two randomized trials have assessed the effects of different recruitment methods on the recruitment rate of older adults into clinical trials. One found that telephone contact significantly increased the recruitment of older adults to a physical activity study compared with methods without telephone contact,[33] and the second, focused on the recruitment of older African-American men for a cancer screening trial, found that the strategy with the highest rate of face-to-face contact with study participants produced the highest recruitment yield.[34] A third trial assessed whether a comprehensive educational intervention (involving standard information plus an educational seminar, educational materials, a list of available protocols for use on charts, a monthly e-mail and mail reminders for 1 year and a case discussion seminar) directed to physicians and other members of the medical and research team would improve the accrual of older persons to cancer treatment trials.[35] No effect of this intervention could be demonstrated. The authors suggested several reasons for the inefficacy of the programme, such as low intervention intensity, high baseline accrual rates (all of the centres in the trial belonged to a cancer network) and closure of several high-accruing protocols during the study. No other trials were identified that have tested a strategy specifically aiming to improve the involvement of older adults in clinical trials.

Other proposed strategies

Table 132.1 summarizes some of the other strategies, not yet tested in randomized controlled trials, that could be used to improve the participation of older adults in clinical trials based on the barriers identified in the previous section and other suggestions from the literature.[11,30,36–38]

Conclusion

Older adults need to be included in clinical trials so that treatments can be adapted to the physiological changes and comorbidities commonly present in this population and to study the prevention, management and treatment of age-related syndromes or diseases. Currently, older adults are under-represented in clinical trials and so their rate of participation needs to be increased. Further work is required to identify strategies that may facilitate the participation of older people in clinical trials. This will require further determination of the differences between study participants and non-participants and identification of modifiable barriers or facilitators to participation. The effectiveness of new strategies aiming to increase enrolment or participation must be tested in randomized controlled trials.

Key points

- Traditionally, older people have been excluded from clinical trials.
- The level of participation of older adults in clinical trials is highly disproportionate to their level of health burden, healthcare expenditure and prescription drug use.
- Even if the inclusion and exclusion criteria allow their participation, investigators may be deterred from enrolling older subjects due the numerous methodological difficulties of conducting research with older people, for example, high rates of dropout or death, selection bias and the presence of comorbidities and multiple medicines (polypharmacy).
- The effectiveness of new strategies aiming to increase enrolment of older adults or their participation must be tested in randomized controlled trials.

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CHAPTER 133

Restraints and immobility

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Introduction

Immobility is strongly associated with functional decline among older adults. Restrictive devices such as physical restraints and siderails deter mobility. Despite a growing body of literature documenting the negative consequences associated with immobilizing older adults with restrictive devices, the practice persists in both acute and long-term healthcare settings, where most healthcare providers continue to believe that restraints are an effective strategy in keeping older adults safe. This chapter provides an overview of the effects of immobility, with emphasis on the consequences of prolonged physical restraint and restrictive siderail usage. Finally, clinical strategies and organizational approaches to replace restraints and restrictive siderails and the evidence to support their use are presented.

Immobility

Immobility is the restriction of time spent out of bed (or chair) by medical orders, restrictive devices, chemical restraints, lack of mobility aids, human assistance or encouragement. Immobility has been correlated with muscle atrophy, loss of muscle strength and endurance, bone loss, joint contractures and problems with balance and coordination that lead to an increased incidence of falls.[1–3] Moreover, reduced bone mass, which is a consequence of decreased weight-bearing and physical activity, can contribute to the increased likelihood that falls will result in serious injury.[4] Other secondary effects of immobility include increased risk of infection, new pressure sores, contractures and functional incontinence. Table 133.1 lists the effects of immobility.[5,6]

It is well documented that functional decline, including new walking dependence, occurs in one-third to half of older hospitalized patients.[7–12] Functional decline or 'deconditioning' refers to the loss of the ability to perform basic activities of daily living. Attributed primarily to the effects of immobilization by 'forced bed rest, immobilizing devices (e.g. catheters), restraint use and lack of encouragement of independence in self-care',[13] functional decline has been correlated with numerous negative consequences. As many as one-third of older patients are restricted to bed rest or chair rest during hospitalization.[7] A systematic review of 30 studies examining correlates of functional decline found that between 15 and 76% of hospitalized elders experience diminished performance in at least one activity of daily living at discharge. Of those with decline at discharge, only half will recover function at 3 months post-discharge and, for many, this decline will result in permanent loss of independent living.[8,12,14–16] Functional decline is considered a profound marker of morbidity and mortality,[17,18] resulting in longer lengths of stay, greater costs and increased rate of nursing home (NH) placement.[8,12,19,20]

One of the most physically debilitating effects of immobility is the development of contractures. The word contracture is used to describe both muscle fixation and joint fixation. Contractures are prevalent in the NH setting, as they are a major consequence of immobility. They develop out of a complex process that involves structural changes that cause shortening in the muscles adjacent to a major joint. Together, the muscles and joint become fixated in a position of flexion. It is thought that this creates a permanent decrease in range of motion.

There is strong support in the literature linking prolonged physical restraint use with the consequences of immobility.[10,19,21,22] This process, labelled 'spiralling immobility' by Tinetti and Ginter,[23] creates a 'catch-22' situation in which an older person, perceived to be at risk of falling, is restrained to prevent falling and is then unable to ambulate again, independently or safely, due to the immobilizing consequences of physical restraint. Other restrictive devices (e.g. full enclosure siderails) or practices (e.g. lack

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Table 133.1 Effects of immobility.

Musculoskeletal
Muscle atrophy
Loss of muscle strength and endurance
Osteoporosis
Joint contractures
Problems with balance and coordination
Gastrointestinal
Constipation
Impaction
Integumentary
Pressure ulcers
Respiratory
Pneumonia
Atelectasis
Cardiovascular
Deep vein thrombosis
Pulmonary embolism
Orthostasis

of assistance out of bed) also contribute to immobilization. Table 133.2 summarizes the effects of physical restraints and siderails.

Physical restraints

Physical restraints are defined as 'any manual method or physical or mechanical device, material or equipment attached or adjacent to the individual's body that the individual cannot remove easily which restricts freedom of movement or normal access to one's body'.[24] Examples of physical restraints include chest/vest, pelvic, combination of wrist, mitt or ankle, and also geriatric chairs with fixed tray tables and cushion tables in wheelchairs. These devices are generally not easily removed by the older adult.[25]

Restraint use in NHs varies widely among countries and institutions. Restraint practice patterns are attributed to cultural backgrounds and ethical views.[26] In general, the restraint use in Denmark, Iceland and Japan is low with less than 9% of NH residents restrained at any time.[26] Between 15 and 17% of residents were restrained in France, Italy and Sweden. Spain demonstrated almost 40% of residents restrained. Similarly, Germany reported restraint use at 26%[27] and Switzerland at 40%.[28] Another study found that 24% of older adults are restrained in Sweden[29] and at least 52% of residents in Dutch NHs are restrained.[30]

Combined with the research and heavy regulatory oversight in the USA, the prevalence of restraint use among NH residents dropped from 9.7% in 2001 to 5.5% in 2007.[31] However, restraint use continues to vary widely throughout the USA,[32] with some regions reporting almost 20% usage[33] while others continue with even higher usage.[34]

Table 133.2 Negative effects of physical restraints and siderails.

Musculoskeletal
Immobility
Contractures
Falls
Decreased muscle mass, tone, strength
Osteoporosis
Fractures
Rhabdomyolysis
Neurological
Brachial plexus injury
Axillary vein thrombosis
Compressive neuropathy
Cardiovascular
Stress-induced cardiac arrhythmias
Orthostasis
Dependent oedema
Psychological
Depression
Agitation
Increased confusion
Integumentary
Pressure ulcers
Skin tears, bruises, abrasions
Cellulitis
Gastrointestinal/genitourinary
Incontinence
Constipation
Infectious disease
Nosocomial infections
Miscellaneous
Strangulation/death
Entrapment
Asphyxiation
Hyperthermia

Spurred by the practice shift in the NH setting, in American hospitals, the prevalence varies from 3.4 to 24.3% in non-intensive and intensive care settings, respectively.[35] The past two decades have shown an overall decrease in physical restraint use in acute care and a change in practice patterns.[36,37] In hospitals, restraint use is more often employed to prevent treatment interference than to avert falls, thus arm/limb restraints prevail over chest/vest restraints.[38–40] A chair that prevents rising is the most common form of restraint while limb restraints are the least commonly used.[41] Trunk restraints are more prevalent in Sweden and the USA than other restraint types.[26] In The Netherlands, Germany and Switzerland, siderails are reported as being the most commonly used form of restraint.[42] In addition to decreased restraint usage over the past 30 years, restraints are now 'less restrictive' compared with previous decades; wheelchair cushions and seat belts are more often used than the more restrictive vest restraints.

Siderails

Siderails, also referred to as bed rails, cotsides, guardrails, safety rails or sideboards, are adjustable metal or rigid plastic bars that attach to the bed and come in a variety of sizes.[25] Beds include bilateral, full-length siderails or four 'half' or 'split' siderails, allowing diverse combinations of rails from one upper rail to both upper and lower rails.[43] Siderails are defined as restraints or 'restrictive' devices when used to impede a patient's ability to get out of bed voluntarily.[44] Since the use of restraints in bed has been drastically reduced in both NHs and hospitals, siderails have become the most frequently used restraint to prevent older adults from independent or accidental egress from bed.[45–47]

Similarly to physical restraints, siderail use varies among countries and institutions. A study conducted in a British hospital reported that 8.4% of patients had full-length siderails raised and a multisite study in English and Welsh hospitals showed full-length siderail use varying between 12.2 and 38.9%.[48] There are no national statistics available for siderail prevalence in American NHs and hospitals;[25] however, several studies report rates of restrictive siderail use ranging from 18 to 64%.[46,49–51] The Royal College of Nursing issued guidelines aimed at further reduction of restraints, and bedrails are listed as the most likely form of restraint.

The continued use of both restraint and siderail usage is based on embedded practices of healthcare providers who for decades have linked these devices to patient safety and protection.[52,53] As a result, efforts to reduce their use have occurred through regulatory oversight and guideline development for the assessment of risk. For example, the US Food and Drug Administration (FDA) has issued several guidelines, including the most recent 'A Guide for Modifying Bed Systems and Using Accessories to Reduce the Risk of Entrapment'.[54] The United States Centers for Medicare and Medicaid Services (CMS) (formerly the Health Care Financing Administration) has guidelines to NHs that classify siderails as restraints when they prevent voluntary egress.[55] These guidelines emphasize that restraints are defined according to their functional application as any device, material or equipment that inhibits mobility or change in position and are not easily removed by the person.[56] Similarly, the 1999 CMS Hospital Conditions of Participation and 2001 JCAHO standards redefined siderail use as restraints for hospitals using this functional definition.[57] Since then, the FDA Hospital Bed Workgroup has created guidelines that describe assessment techniques for implementing siderails, and also developed the Bed Safety Tool Kit, which includes information and tools aimed at reducing the rate of entrapment in siderails.[58] Based on the American guidelines, Canada issued 'Adult Hospital Beds: Patient Entrapment Hazards, Side Rail Latching Reliability and Other Hazards' in 2008, which provides similar recommendations.[59]

Risk factors and justification

Use of restrictive devices depends on three factors: patient characteristics, organizational attributes and healthcare providers' justification. Prevalence of restrictive devices varies with age, functional status and cognition.[60] Greater age, worsened physical health, a previous fall and the presence of depression or other psychiatric disorders have been associated with restraint use.[49,61,62]

Impaired cognition is the most significant patient factor associated with restraint and siderail use.[33,45,53,63,64] Among ambulatory NH residents, a restraint prevalence of 37% was reported in confused residents, whereas non-confused residents were virtually never restrained.[64] Confused older adults and elders are also the most likely to be restrained in hospitals.[65,66]

Castle *et al*. reported that organizational attributes, rather than patient factors, were more predictive of restraint use.[67] These include high nursing aide–patient ratios, reduced occupancy rates and prospective Medicaid reimbursement. Similarly, in hospitals, high utilization of licensed practical nurses rather than registered nurses and nurse staffing patterns on weekend shifts are strongly associated with restraint use.[66] The American statistics are in direct contrast, however, to a recent European study that revealed job characteristics (i.e. high workload) and ward characteristics (i.e. low percentage of nurses) were less significant in predicting restraint use than resident factors.[42] High risk of self-harm or injury to staff is a common reason cited for patient restraint.[68] Other reasons include paradigms that restraint use is generally appropriate and that siderails are only moderately restrictive.[42]

Justification for restraints is also based on the healthcare providers' view that these devices prevent vulnerable older adults from injury secondary to falls, behavioural symptoms or treatment interference. The most common reason cited for restraint and siderail use is prevention of falls,[25] and other common reasons include mobility aid and prevention of wandering.[48] There is no empirical evidence, however, to support the use of these devices to prevent falls.

Numerous studies demonstrate a significant incidence of falls and injury among restrained confused patients in both NH and hospital settings.[64,69–72] In addition, another study examining the relationship between restraint use and falls among NH residents found that restraints were not associated with a significantly lower risk of falls or fall-related injuries.[64]

There is also no evidence to support the use of restrictive siderails to prevent falls. One NH study examined resident outcomes associated with consistent restrictive siderail status when compared with residents with no or

non-restrictive siderail use for 1 year.[46] Controlling for cognition, functional and behavioural status, the study found no indication of a decreased risk of falls or recurrent falls with restrictive siderail use. Similarly, a retrospective hospital-based study found that the incidence of falls from bed with siderails elevated was equal to or higher than the outcome when siderails were not elevated. Those patients with impaired cognition status were found to be the most likely to fall from bed when the siderails were elevated.[47]

Another major reason that healthcare providers choose restrictive devices is to reduce or control behavioural symptoms. Interestingly, although restraints are employed to 'treat' these symptoms, the use of these devices is strongly correlated with physical or verbal aggression, especially among those with dementia.[73–76] Delirium has also been found to be highly correlated with restraint use in several large-scale studies.[77–79] The usage of restrictive devices to manage behavioural symptoms in NHs or medical/surgical (non-psychiatric) care settings is strongly prohibited.

Behavioural symptoms, such as anxiety, agitation, physical aggression and delirium, may result in patient interference with medical treatments. Treatment interference refers to both removal and manipulation of a monitoring or treatment device (e.g. feeding tubes, urinary catheters, intravenous lines, oxygen therapy).[80–83] This can be especially dangerous when the treatment or device fulfils a life-saving or life-maintaining function such as mechanical ventilatory support. Hand restraints may not prevent unplanned extubations in agitated patients.[84] Since many of those with unplanned extubations do not require reintubation,[84,85] restraints may be a marker of insufficient sedation that requires more attention to implementation of evidence-based guidelines for sedation of intubated patients.[86,87] The lack of evidence to support routine restrictive device usage to prevent falls and treatment interference or reduce behavioural symptoms is thus compounded by the numerous complications associated with use of these devices.

Complications

The use of restrictive devices is not without risk. In the 1980s and 1990s, research describing the negative physical and psychological sequelae associated with restrictive devices was the major impetus for changing the practice in hospitals and NHs.[88] Psychologically, restrained older adults experience anger, humiliation, depression and low self-esteem.[89–91] Additionally, the use of restraints may convey feelings of punishment, emotional harm and patient suffering.[68]

As described earlier in this chapter, the most common physical consequence of prolonged restraint or siderail use is immobility.[10,19,21,22,33] Other harmful medical outcomes associated with restraint include hyperthermia,[92] rhabdomyolysis,[93] brachial plexus injury,[94] axillary vein thrombosis,[95] compressive neuropathy,[96] Hess's sign[97] and stress-induced cardiac arrhythmias.[98] Furthermore, siderails have been identified as a vector for nosocomial infections. Microbes cultured from siderails have been associated with subsequent integumentary and respiratory ailments.[99–104]

Although less common, restrictive devices have also been associated with fatal outcomes such as thromboembolic disease[105] and strangulation and asphyxiation.[98,106,107] Strangulation can occur due to improper application of a vest restraint or when an older adult with a vest restraint slips between two half rails. Asphyxiation results from gravitational chest compression when an older adult is suspended by a vest or belt restraint in a bed or chair.[108,109] Asphyxiation can also occur if a person is entrapped within siderails or when patients become entrapped between theapeutic overlay air mattresses and siderails.[110]

Entrapments occur through the siderail bars, through the space between split siderails, between the siderail and mattress or between the head or footboard, siderail and mattress.[111] Persons at high risk for entrapment include older adults with pre-existing conditions such as altered mental status (dementia or delirium), restlessness, lack of muscle control or a combination of these factors.[112,113] More recently, cases of asphyxiation deaths due to patients becoming trapped between therapeutic overlay air mattresses and siderails have been reported.[110] These negative consequences associated with restraint use have served as an impetus for research aimed at identifying alternative 'best practices' to restrictive devices.

Outcomes of restrictive device reduction

Several studies have described the relationship between restraint reduction and fall/injury rates. In all of these studies, significant reduction in restraints and siderails occurred without increases in falls or fall-related injuries.[50,70,114–118] Although none of the studies represent a randomized clinical trial, no significant differences were found in the number of patients falling prior to or following the reduction of physical restraint use. Further, the studies demonstrated no statistically significant difference in falls compared with historical controls when restrictive siderails are removed.[119]

Fall-related injuries are rarely examined statistically, since the number of subjects required is often cost prohibitive for most research studies. Fall-related minor injury in older persons, however, has significant implications for morbidity and mortality.[120] Capezuti *et al*. reported that continued restraint use (versus restraint removal) was the only characteristic to increase significantly the risk of fall-related minor injury (bruises, abrasions, certain sprains and other soft tissue injuries that do not result in hospitalization or bed rest).[70] In summary, results from studies of

restrictive device reduction efforts have demonstrated that they can be removed without negative consequences.

The positive outcomes associated with restrictive device reduction may represent not only the safe removal of these devices, but also the effectiveness of interventions aimed at decreasing the likelihood of falling and injuries. Both individual alternatives and the most effective strategies used to implement these interventions have been evaluated in NH and hospital settings.

Approaches to reduce restrictive device usage

Optimal resolution requires multiple interventions that rely on coordination via interdisciplinary dialogue and action.[121] Comprehensive assessment, coordinated care management and individualized intervention plans targeting identified risk factors have been found to be the most successful strategies to reduce restrictive devices.

'Best practice' approaches to restrictive device reduction are described in the literature or by professional associations as clinical practice guidelines for use in the NH and acute-care hospital.[47,58,108,122–124] Professional standards and governmental and accreditation regulations emphasize that a decision to use physical restraints and/or siderails should only be made after clinical evaluation and interdisciplinary care planning determines the purpose for the intervention. Further, alternatives to restrictive devices should be implemented and evaluated prior to initiating restraints. Thus, a thorough assessment is necessary in the following situations: in patients who are at high risk for application of physical restraints or siderails, prior to and during restraint reduction efforts, or in situations where the provider is assessing the continued need for restrictive devices.

Multidisciplinary collaboration is an important part of any evaluation regarding the use of restraints and siderails. There is also an indication that, due to the differences in staff opinions regarding restraint use, cultural sensitivity is necessary in designing interventions to reduce the use of physical restraints.[42] The following sections describe clinical approaches that reduce the likelihood of restrictive device use.

Promote mobility

Maintaining physical activity in hospitalized elders and NH residents is crucial to preventing the harmful effects of immobility. Careful consideration is warranted when ordering bed rest. The ability to move around in bed and to transfer and ambulate safely is also important to prevent falls and injuries.[125] The assessment should include the patient's ability to perform the skills necessary for safe mobility and transfer, including the need for assistance and assistive devices (e.g. walkers, canes). If there are problems, then a physical or occupational therapist should be consulted. Rehabilitation therapists may suggest transfer devices to enable or assist in safe transfer and promote stability when standing, which may include a trapeze, transfer pole or bar or raised one-quarter or half length siderail directly attached to or adjacent to the top of the bed. These may also serve as assistive bed mobility devices.

Certain activities by nursing staff promote mobility, such as encouraging or assisting patients with changing position in bed, transferring out of bed to chair and ambulating.[126] Organized group walks around the nursing unit at specific times during the day promote mobility, provide diversion and involve the patient in his/her recovery. Bed and toilet seat height should be adjusted to the patient's lower leg height in order to promote safe transfers.[127]

Facilitate observation

Patients at risk for falls or treatment interference should be located in rooms closer to the nurses' station to facilitate observation. Increased time spent out of rooms in hallways, at the nurses' station or in 'day' rooms with other patients facilitates surveillance. Family and friends should be encouraged to visit, especially during mealtimes and treatments and at night to provide both meaningful distraction and assistance to staff. Providing communal dining when possible serves both this purpose and an opportunity for socialization.

Volunteers or paid 'companions' can be an alternative when families are unable to stay with the patient.[128] This, however, can incur significant cost and must be evaluated in relationship to the potential harm of leaving a patient alone. Patients at high risk for restraint require frequent observation, especially in a new environment. Hence these patients may need to be targeted for 'one-on-one' companions if other means of increased staff surveillance are not available.

An open intercom, 'nursery' or 'baby' monitor will promote audio contact between staff and patients. Video monitoring may be an option in some hospitals, and also motion-sensor lights or alarms in rooms that alert staff that the resident is ambulating in their room unassisted. Elopement control devices are used for 'wanderers' who may walk into unsafe areas. They work similarly to department store tag devices. An identification tag placed on the resident's wrist or ankle will signal the detection monitoring device when the resident walks by it, thus setting off the alarm.[129]

Devices such as alarms are useful; however, staff must be available to respond quickly. There are various types of alarms: pressure-sensor activated, cord activated and patient worn.[130] Pressure-sensor activated alarms sound as shifts in weight occur on a pad placed over the mattress or chair cushion. Alarms worn by patients (usually on the

thigh) are sensitive to resident position changes (e.g. from lying to standing). A call bell or similar device attached to clothing will sound when the resident rises and disconnects the cord from the socket. Alarms require individualization of delay time to minimize number of 'false' alarms. Also, the occurrence of 'nuisance' sounds may increase agitation in confused patients. Models that sound at the nurses' station, light a hallway call system or activate a staff pager reduce nuisance alarms.[130] Some alarms include a voice 'alarm', that is, a tape recorder that can play an individualized message addressing the resident by name and calmly instructing the resident to remain in his/her chair until the nurse arrives to provide assistance.

Offer activities

It is not surprising that patients will attempt to ambulate without assistance or remove tubes when isolated in a room without meaningful activities. Television is not the solution; it may actually incite agitation. Recreation or activities therapists, if available, should be consulted. Family members can be encouraged to bring in favourite music or videotapes, hobby materials (e.g. knitting) or other items that the patient may enjoy. Staff or volunteers can also provide activities based on the patient's interest and cognitive level, for example, towels to fold, magazines to read and stuffed animals to hold. Activities also serve to distract patients from 'investigating' or disturbing tubes, monitor, leads and dressings.[131]

Maintain continence

Often patients attempt to ambulate unassisted because of an urgent need to void. Assess the patient's ability to use a bedside commode or urinal safely, which may reduce the distance travelled to the bathroom and thus reduce falls. Query the patient or nursing staff regarding a change in toileting patterns, including nocturia and bowel and bladder incontinence, which may require further evaluation by a continence specialist.

Promote comfort

Comfort needs include equipment individualized to a patient's medical/functional condition and appropriate pain management. Providing comfortable and individualized seating is a major challenge, especially in the NH setting. In the NH, most patients spend the majority of their day in a wheelchair.[132] The prevalence of wheelchairs in NHs exceeds 50% and many patients spend their time in chairs that do not fit and are uncomfortable.[133] Wheelchairs were originally designed for transport only, not for long periods of sitting. Their sling-back seats do not provide the appropriate support. Seating problems such as poor back support; wheelchair being too tall, heavy or wide; foot rests too high; and the hammock effect of the sling are all associated with pain and agitation.[134] All these effects increase the risk for falling and use of physical restraints, since the patient may be uncomfortable and attempt to transfer unsafely. Many products are available to adapt the chair to the individual resident's seating needs. Other adaptations for the wheelchair include a wedge cushion inserted under the resident's buttocks and thighs, which tilt the resident backwards. A wedge seat prevents the resident from sliding forward. Similarly, leaning to the side is corrected with lateral supports or cushions. Stroke victims with hemiplegia (one-sided weakness) are at risk for shoulder subluxation if the weakened arm slips off the side of the chair. This can be prevented with devices attached to a wheelchair: an arm trough, elevated armrest, lateral arm support or half tray. Patients who spend a considerable time in a wheelchair are to be referred to a physical or occupational therapist for a seating evaluation.[134,135] The patient's comfort in bed can be improved with an overlay mattress cushion, air mattress or sheepskin mattress pads.[136] Pillows and leg separator cushions can be used to facilitate positioning. Heel pads and/or bed cradles are good choices for those with significant peripheral vascular disease or pressure ulcers. Refer to a wound, ostomy and continence (WOC) nurse or physical therapist for device recommendations. Chronic and acute pain is common in older adults; however, many are inadequately treated. Pain management includes both administration of analgesics and other treatments (e.g. physical rehabilitation exercise, relaxation training, biofeedback, hot packs). Older adults with dementia have the same types of medical conditions as non-demented elders; however, evidence suggests that they are less likely to receive pain treatment.[137] Thus, routinely scheduled analgesia is strongly recommended.[138] Since the patient may not be able to report or describe pain, observation of non-verbal signs of pain is necessary. Indicators of pain in cognitively impaired elders include facial grimacing, physical aggression, pacing, uncooperativeness and restless behaviour.[139]

Investigate mental status changes

It is important to assess changes in mental status since impaired cognitive status is highly associated with increased risk of falling and use of restrictive devices.[140] New behavioural symptoms (e.g. physical aggression) should first trigger a comprehensive evaluation of potential physical and/or environmental causes prior to initiating any physical or chemical restraint. Behaviour can be used to communicate a need, threat to self-esteem, a state of arousal or anxiety.[60] Confused older adults may not be able to express verbally that they are experiencing pain or have the need to use, for example, the toilet and will

often act out with some form of behaviour (e.g. anxiety, wandering).[141,142] Complicated cases could require a geriatric psychiatry consultation.

Address fall risk

If a patient has been deemed at risk of falls or has fallen, then a thorough evaluation of amenable risk factors contributing to future risk should be conducted. Falls, especially sudden onset of repeated falls, may indicate underlying acute pathology, such as infection, hypoglycaemia or dehydration.[143] Evaluation of fall risk is addressed by several medical associations and academic institutions, such as the American Geriatrics Society and British Geriatrics Society,[144] American Medical Directors Association and The American Health Care Association,[145] the University of Iowa[146] and Assessing Care of Vulnerable Elders (ACOVE) Project on Falls Prevention.[147]

Medications are associated with an increased risk for falling. All types of psychoactive medications (hypnotics, antidepressants, anxiolytics, benzodiazepines and antipsychotics) have consistently been linked to an increased risk for falling[148] due to the risk for adverse side effects such as syncope and orthostasis.[149–151] Ray *et al*.[152] identified benzodiazepine users in NH residents having a rate of falls 44% greater than those not taking benzodiazepines. Additionally, fall risk increased with a higher dose of benzodiazepine use. Those on antidepressants, both tricyclic antidepressants and selective serotonin-reuptake inhibitors, have a higher risk for falls compared with non-users.[149,153] Therefore, prescription of these medications must be carefully balanced against the risk of falls and related injuries. A general rule of geriatric pharmacology is to minimize the number of medications, assess the risk and benefit of each medication and use those medications with the shortest half-life, least centrally acting or least associated with hypotension and at the lowest effective dose. A pharmacist may be consulted to uncover potential drug–drug interactions and to make suggestions regarding inappropriate drug usage.

Environmental modifications may reduce falls. For example, a non-skid mat placed at the side of the bed and/or toilet and raised-tread socks can reduce the likelihood of slipping.[125] For those patients unable to stand safely but who may accidentally roll out of or unsafely exit from bed, bed bumpers on mattress edges, concave mattresses, pillows, 'swimming pool noodles' or rolled blankets under the mattress edge demarcate bed perimeters.[132]

Reduce injury risk

Since falling on to hard surfaces may increase the likelihood of fractures, a bedside cushion such as an exercise mat or an egg crate foam mattress may be used to reduce impact.[136] Hip protector pads are the best studied single intervention strategy for fall-related injury prevention among high-risk older adults. Hip protectors are pads held in place next to the greater trochanter that reduce the force transmitted in a fall.[154] There are several large-scale, randomized and controlled clinical trials that demonstrate a strong association between reduced hip fracture rates and hip pad usage in community-dwelling elders.[155,156] However, their use in NH settings is more controversial, as the Cochrane Systematic Review on the use of hip protectors suggests that lack of compliance with wearing the hip protector pad is often due to discomfort and thus decreases their potential efficacy in reducing injury.[157] This is consistent with other literature, suggesting that further research into the use of hip protector pads in nursing homes would be helpful.[158] Compliance with wearing the hip protectors is a significant problem due to discomfort and poor fit.[157,158] Incontinent NH residents experience discomfort when wearing the garment.[159,160] For residents with a history of climbing around or over siderails, reducing the risk of an entrapment injury is paramount. Since restraint-related deaths can occur in less than a few minutes, these devices necessitate increased, not decreased, staff observation. Inspect bed frames, siderails and mattresses to identify possible entrapment areas.[58,112]

Address treatment interference

Discomfort caused by unstable tube placement can increase the chances of self-removal or disruption of tube performance. Commercial tube holders to stabilize Foley catheters, intravenous lines and feeding, drainage and endotracheal tubes should be used.[161] Waterproof tape can decrease accidental extubations.[162] Devices can be camouflaged by hiding them under cloth (e.g. abdominal binder), undergarments or clothing, sheets or blankets, to divert the patient's attention from a treatment. Infusion sites can be covered with commercial holders, bandages or stockinettes.[161] For confused patients who 'pick' or who are seeking tactile stimulation, provide fabric, stuffed animals or an activity apron. Finally, periodically assess the need for any treatment such as bladder catheterization or intravenous fluids; determine if it can be discontinued or if a less invasive treatment can replace it.[60]

Advanced practice nursing interventions

Advanced practice nursing (APN) interventions can be effective in reducing or eliminating restrictive restraint use in NH settings.[163,164] Although the APN role can help reduce restraint use, adherence to these policies over an extended period of time is largely influenced by administrative support.[117] The APN can support NHs in reducing

restraint use by utilizing individualized assessments and a complex clinical decision-making process. Additionally, APNs can use their roles as staff educators and clinical nursing consultants to help address staff and resident perceptions about the use of restrictive siderails.[163] The presence of research staff in a clinical area and familiarization of nursing staff with current research and best practices can also generate a better understanding of the policies regarding the use of siderails and restraints.[165]

Staff education programmes

The literature on the use of educational interventions to affect staff attitudes and knowledge on the use of physical restraints is conflicting. One cluster-randomized controlled trial showed that a 6 month educational programme for nurses was successful in reducing the use of physical restraints and increasing staff knowledge.[166] However, another similar study showed that a shorter 2 month educational programme combined with nurse specialist consultation does not prevent the use of physical restraints.[167] Short-term educational programmes may only influence restraint use for the length of the study period and may not have any long-term effects.[30] These results indicate that longer educational interventions may be more successful in changing staff attitudes towards restraint use and also lend to the idea that interventions at an organizational level may be necessary in order to instigate change.

The need for long-term organization-level educational programmes is emphasized by an Australian study that focused on educating management personnel on the use of restraints in NHs.[168] This allows for knowledge dissemination to all staff members and encourages the use of current research. Likewise, Moore and Haralambous[169] found that NH staff at all levels require education in evidence-based practice surrounding restraint use.

Conclusion

Physical restraints and restrictive siderails play a limited role in providing medical care to frail older patients. Rather, use of restraints and siderails leads to the harmful effects of immobility. Several studies have demonstrated that restraints and siderails can be removed without negative consequences. Primary care providers can reduce the use of physical restraints and restrictive siderails by conducting a careful assessment and implementing appropriate individualized interventions. The use of non-restrictive measures has been correlated with positive patient outcomes and helps to promote mobility and functional recovery. Most of these products, however, have not been prospectively evaluated in large randomized clinical trials for their individual contribution to reduction of falls or treatment interference.[119,144] Further research on the efficacy of individual interventions that replace restrictive devices and improve mobility is still needed.[170]

Key points

- Immobility is correlated with functional decline, which is considered a profound marker of morbidity and mortality.
- There is strong support in the literature linking physical restraint and restrictive siderail use with the consequences of immobility.
- The continued use of both restraint and siderail usage is based on embedded practices of healthcare providers who for decades have linked these devices to patient safety and protection.
- Restrictive devices are associated with numerous negative outcomes, including strangulation and asphyxiation.
- Research demonstrates that restrictive devices can be safely eliminated.

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CHAPTER 134

Centenarians

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An optimistic view

The prevalent notion that 'the older you get, the sicker you get' often leads the lay public to assume that those who achieve exceptional longevity must have numerous age-related illnesses that translate into a very poor quality of life. Among researchers and clinicians, the observation that the prevalence and incidence of dementia increase with age leads many to assume that dementia is inevitable for those who survive to age 100 years and older.[1,2] For example, the East Boston Study indicated that almost 50% of people over the age of 85 years have Alzheimer's disease.[3,4] Over the past decade or so, however, significant light has been shed on this assumption, with a number of nonagenarian and centenarian studies addressing the prevalence and incidence of dementia amongst the oldest old; these are summarized in Table 134.1.

As most of the studies noted in Table 134.1 indicate, dementia is not inevitable with very old age. Conservatively, ~15–20% of centenarians are cognitively intact. Furthermore, when dementia does occur, it tends to do so very late in life. In one study, over 90% of the centenarians did not experience functional impairment until the average age of 93 years.[18] The Heidelberg Centenarian Study proposed that those who develop dementia at extreme age have a shorter period of functional decline prior to the end of their lives.[16] In their review of the neuropathology literature amongst studies of nonagenarians and centenarians, von Gunten *et al*. concluded that the absence of Alzheimer's-related pathology in some of these individuals indicates that this disease is not a necessary consequence of ageing.[19] There have also been observations by several groups that in some centenarians, there is a disassociation between advanced pathology and clinical presentation, which suggests the presence of functional reserve or some form of adaptive capacity that allows these individuals to do better than expected given the degree of pathology on postmortem examination. The authors conclude that at least some centenarians have some form of resistance to Alzheimer's disease, the underlying cause of which has yet to be determined. Hence centenarians are of interest in the study of dementia not only for the fact that some of them escape dementia, but also because most of them markedly delay the clinical expression of the disease until very late in their exceptionally long lives.

Compression of morbidity versus disability

The compression of functional impairment towards the end of life that is observed among centenarians would at first glance appear to be consistent with James Fries's compression-of morbidity hypothesis.[20] Fries proposed that as the limit of human lifespan is approached, the onset and duration of lethal diseases associated with ageing must be compressed towards the end of life.[21] Although we found that functional impairment was compressed towards the end of life among centenarians, we noted that some centenarians had long histories of an age-related disease. Perhaps an unusual adaptive capacity or functional reserve allowed some of these persons to live a long time with what normally would be considered a debilitating, if not fatal, disease while delaying its attendant disability and death by as much as decades.[22–26]

Consistent with this observed phenomenon of compression of disability, the Danish Centenarian Study accessed 1997 and 2004 data from the Danish Civil Registration System on nearly 40 000 people born in 1905 and found that centenarians had fewer hospitalizations and shorter hospital stays compared with other members of their birth cohort who died at younger ages. It was concluded that centenarians are a useful cohort for the study of healthy ageing.

To explore this hypothesis in our centenarian sample, we conducted a retrospective cohort study exploring the timing of age-related diseases amongst individuals achieving exceptional old age.[27] Three profiles emerged from the analysis of health history data. Some 42% of the participants were 'survivors', in whom at least one of the 12 most

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Table 134.1 Dementia studies of nonagenarians and centenarians.

Study	Comments
Dutch population-based centenarian study	10 centenarians in a population of 100 000 people were all noted to have clinically evident dementia.[5] Expansion of the study to a population of 250 000 led to finding 15 of 17 centenarians as having dementia[6]
Swedish population-based study of people aged ≥77 years	The prevalence of dementia amongst the 94 subjects aged ≥95 years was 48% (30% for men and 50% for women)[7]
Canadian Study of Health and Ageing	Dementia prevalence of subjects aged ≥95 years ($n = 104$) was 58%. The rate of increase in prevalence slowed at very advanced ages[1]
Study of Japanese Americans in King County, Washington	Dementia prevalence for subjects aged ≥95 years was 74%[8]
MRC-ALPHA Study, of older people in Liverpool	Dementia prevalence amongst centenarians was 47%[9]
Northern Italian Centenarian Study	Dementia was diagnosed in 62% of 92 centenarians[10]
Finnish population-based centenarian study	56% of 179 centenarians had cognitive impairment[11]
Meta-analysis of nine epidemiological studies of dementia among people aged ≥80 years	Prevalence of dementia levelled off at around age 95 years at a rate of 40%[12]
New England Centenarian (population-based) Study	Cognitive impairment prevalence was 79%[13]
Danish Centenarian Study	Dementia prevalence was 67%[14]
Coordinated study of dementia prevalence among centenarians in Sweden, Georgia (USA) and Japan	Dementia prevalences ranged from 40 to 63%[15]
Heidelberg Centenarian Study	Cognitive impairment prevalence was 75%[16]
French Centenarian Study	Dementia prevalence was 65% among female and 42% among male centenarians[17]

common age-associated diseases was diagnosed before the age of 80 years; 45% were 'delayers', in whom one of these age-associated diseases was diagnosed at or after the age of 80 years, which was beyond the average life expectancy for their birth cohort; and 13% were 'escapers', who attained their 100th birthday without diagnosis of any of the 10 age-associated diseases studied. That most centenarians appear to be functionally independent through their early 90s suggests the possibility that 'survivors' and 'delayers' are better able to cope with illnesses and remain functionally independent compared with the average ageing population. Therefore, in the case of centenarians, it may be more accurate to note a compression of disability rather than a compression of morbidity. As would be expected, this is not generally the case with illnesses associated with high mortality risks. When examining only the most lethal diseases of the elderly, such as heart disease, non-skin cancer and stroke, 87% of males and 83% of females delayed or escaped such diseases (relatively few centenarians were 'survivors' with such diseases). These results suggest there may be multiple routes to achieving exceptional longevity. The survivor, delayer and escaper profiles represent different centenarian phenotypes and probably also different genotypes. The categorization of centenarians into these and other groupings (for example, cognitively intact persons or smokers without smoking-related illnesses) should prove useful in the study of factors that determine exceptional longevity.

Nature versus nurture

The relative contribution of environmental and genetic influences to life expectancy has been a source of debate. Assessing heritability in 10 505 Swedish twin pairs reared together and apart, Ljungquist *et al*.[28] attributed 35% of the variance in longevity to genetic influences and 65% of the variance to non-shared environmental effects. Other twin studies indicate heritability estimates of life expectancy between 25 and 30%.[29,30] A study of 1655 old order Amish subjects born between 1749 and 1890 and surviving beyond age 30 years resulted in a heritability calculation for lifespan of 0.25.[31] These studies support the contention that the life spans of average humans with their average set of genetic polymorphisms are differentiated primarily by their habits and environments. Supporting this idea is a study of Seventh Day Adventists. In contrast to the American average life expectancy of 80 years, the average life expectancy of Seventh Day Adventists is 88 years. Because of their religious beliefs, members of this religious faith maintain optimal health habits such as not smoking, a vegetarian diet, regular exercise and maintenance of a lean body mass that translate into the addition of 8 years to their average life expectancy as compared with other Americans.[32] Given that in the USA 75% of persons are overweight and one-third are obese,[33] far too many persons still use tobacco[34] and far too few persons regularly exercise,[35] it is no wonder that

our average life expectancy is about 8 years less than what our average set of genes should be able to achieve for us.

Of course, there are exceptions to the rule. There are individuals who have genetic profiles with or without prerequisite environmental exposures that predispose them to diseases at younger ages. There is also a component of luck, which good or bad, plays a role in life expectancy. Finally, there is the possibility that there exist genetic and environmental factors that facilitate the ability to live to ages significantly older than what the average set of genetic and environmental exposures normally allow. Because the oldest individuals in the twin studies were in their early to mid-80s, those studies provide information about heritability of average life expectancy, but not of substantially older ages, for example, age 100 years and older. As discussed below, to survive the 15 or more years beyond what our average set of genetic variations is capable of achieving for us, it appears that people need to have benefited from a relatively rare combination of what might be not-so-rare environmental, behavioural and genetic characteristics, which are often shared within families.

Studying Mormon pedigrees from the Utah Population Database, Kerber *et al*.[36] investigated the impact of family history upon the longevity of 78 994 individuals who achieved at least the age of 65 years. The relative risk of survival (λ_s) calculated for siblings of probands achieving the 97th percentile of 'excess longevity' (for males this corresponded to an age of 95 years and for women to an age of 97 years) was 2.30. Recurrence risks among more distant relatives in the Mormon pedigrees remained significantly greater than 1.0 for numerous classes of relatives, leading to the conclusion that single-gene effects were at play in this survival advantage. The Mormon study findings agree closely with a study of the Icelandic population in which first-degree relatives of those living to the 95th percentile of surviving age were almost twice as likely to also live to the 95th percentile of survival compared with controls.[37] Both research groups asserted that the range of recurrent relative risks that they observed indicated a substantial genetic component to exceptional longevity.

To explore further the genetic aspects of exceptional old age, Perls *et al*. analysed the pedigrees of 444 centenarian families in the USA that included 2092 siblings of centenarians.[38] Survival was compared with 1900 birth cohort survival data from the US Social Security Administration. As shown in Figure 134.1, female siblings had death rates at all ages that were about half the national level; male siblings had a similar advantage at most ages, although it diminished somewhat during adolescence and young adulthood. The siblings had an average age of death of 76.7 years for females and 70.4 years for males compared with 58.3 and 51.5 years, respectively, for the general population. Even after accounting for race and education, the net survival advantage of siblings of centenarians was found to be 16 years greater than the general population. An increasing genetic role with increasing age at very advanced ages is further supported by the work of Tan *et al*., who noted that the power of a genome-wide association study to discover genes associated with exceptional longevity increases with the age of the subjects, for example from 90s to 100s.[39]

Siblings might share environmental and behavioural factors early in life that have strong effects throughout life. It would make sense that some of these effects are primarily responsible for the shared survival advantage up to middle age. Evidence of effects of early life conditions on adult morbidity and mortality points to the importance of adopting a life course perspective in studies of chronic morbidity and mortality in later life and also in investigations of exceptional longevity.[40–47] Characteristics of childhood environment are not only associated with morbidity and mortality at middle age, but have also been found to predict survival to extreme old age.[48,49] Stone[50] analysed effects of childhood conditions on survival to extreme old age among cohorts born during the late nineteenth century. Key factors predicting survival from childhood to age 110+ years for these individuals, most of whom were born between 1870 and 1889, were farm residence, presence of both parents in the household, American-born parents, family ownership of its dwelling, residence in a rural area and residence in the non-South; characteristics similar to those that had been previously shown to predict survival to age 85 years.[48,49]

In general, however, environmental characteristics such as socioeconomic status, lifestyle and region of residence, are likely to diverge as siblings grow older. Thus, if the survival advantage of the siblings of centenarians is primarily due to environmental factors, that advantage should decline with age. In contrast, the stability of relative risk for death across a wide age range suggests that the advantage is due more to genetic than to environmental factors.

Whereas death rates reflect the current death rate at a moment in time, survival probability reflects the cumulative experience of death up to that moment in a cohort's life history. Thus, a relatively constant advantage from moment to moment (as seen in the relative death rates) translates into an increasing survival advantage over a lifetime [as seen in the relative survival probabilities (RSPs)]. This increase is seen in Table 134.2, which shows the RSPs of the male and female siblings of centenarians at various ages.

By the age of 100 years, the relative survival probability for siblings of centenarians is 8.2 for women and 17 for men. From the analysis of death rates, we know that the siblings' survival advantage does not increase as the siblings age. Rather, the siblings' relative probability of survival is a cumulative measure and reflects their life-long survival advantage over the general population born around the same time. The marked increase in relative survival probability and sustained survival advantage in extreme old age could be consistent with the forces of demographic

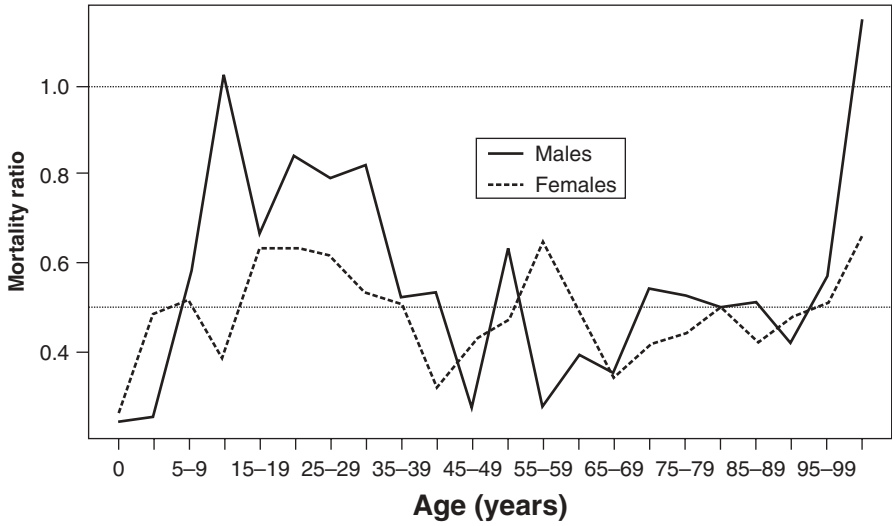

Figure 134.1 Relative mortality of male and female siblings of centenarians compared with birth cohort matched individuals (controls) from the general American population (survival experience of the controls comes from the Social Security Administration's 1900 birth cohort life table).

Table 134.2 Relative survival probabilities (RSP) with 95% confidence intervals (CI) of siblings of centenarians versus the US 1900 birth cohort.

Age	Males			Females		
(years)	RSP	Lower 95% CI	Upper 95% CI	RSP	Lower 95% CI	Upper 95% CI
20	1.00	1.00	1.00	1.00	1.00	1.00
25	1.00	0.99	1.01	1.01	1.00	1.02
60	1.18	1.15	1.21	1.12	1.09	1.14
65	1.29	1.25	1.33	1.16	1.13	1.19
70	1.48	1.42	1.53	1.24	1.21	1.28
75	1.68	1.60	1.77	1.36	1.31	1.41
80	2.03	1.90	2.16	1.54	1.47	1.60
85	2.69	2.47	2.91	1.83	1.73	1.93
90	4.08	3.62	4.54	2.56	2.39	2.74
95	8.35	6.98	9.71	4.15	3.73	4.57
100	17.0	10.8	23.1	8.22	6.55	9.90

selection, in which genes or environmental factors (or both) that predispose to longevity win out over those that are associated with premature or average mortality. The substantially higher relative survival probability values for men at older ages might reflect the fact that male mortality rates are substantially higher than female mortality rates at these ages and, therefore, that men gain a greater advantage from beneficial genotypes than women do. Another possibility is that men require an even rarer combination of genetic and environmental factors to achieve extreme age than women do.[51] Either possibility could explain why men make up only 15% of centenarians.

Centenarian offspring: following in the footsteps of their parents

The familiality of exceptional longevity demonstrated amongst centenarians and their siblings appears to extend also to the offspring of centenarians. Centenarian offspring currently in their 70s and 80s have approximately half the relative prevalence of hypertension, diabetes and cardiovascular disease (including coronary artery disease, myocardial infarction, congestive heart failure and/or arrhythmia) and cardiovascular risk factors compared with controls whose parents died at or before the average life expectancy of their birth cohort or to spousal controls.[52,53]

Among the centenarian offspring who did develop these conditions, the age of onset was significantly delayed compared with the age at onset for controls.[54] Examining the causes of death for deceased centenarian offspring and controls, centenarian offspring had a 62% risk reduction in all-cause mortality, an 85% risk reduction in coronary heart disease-specific mortality and a 71% risk reduction in cancer-specific mortality.[55] Barzilai *et al*.[56] demonstrated that centenarian offspring, when compared with spousal controls, have favourable lipid profiles. These individuals have significantly larger HDL (high-density lipoprotein) and LDL (low-density lipoprotein) particle sizes than controls.[57] The larger particle sizes are associated with lower prevalences of cardiovascular disease, hypertension and metabolic syndrome and are hypothesized to be predictive for longevity.

In addition to lipid profiles, another biomarker, heat shock protein 70 (HSP70), has been examined in the offspring of centenarians compared with spousal controls. Heat shock proteins, which help to chaperone, transport and fold proteins when cells are exposed to a variety of stresses, may protect against or modify the progression of atherosclerosis. In a pilot study of 20 centenarian offspring and nine spousal controls, Terry *et al*.[58] demonstrated a nearly 10-fold difference in levels of circulating HSP70.

Genetic findings

Centenarians may be rare because a complex set of environmental and genetic variables must coexist for such survival to occur. The first genetic association with exceptional longevity, that has also withstood the test of time and numerous studies, has been the observation that the apolipoprotein E epsilon-4 (apo ε-4) allotype is rare amongst centenarians. Individuals who are homozygous for apo ε-4 have a 2.3–8 times greater risk of developing Alzheimer's disease compared with the general Caucasian population.[59,60] The allelic frequency of apo ε-4 drops off dramatically in the oldest age groups, presumably because of its association with Alzheimer's disease and vascular disease.[61] Interestingly, the effect of apolipoprotein E allotype upon Alzheimer's disease incidence appears to decrease with age at these very old ages.[11]

Richard Cutler, in what is now a classic paper in gerontology, proposed that persons who achieve extreme old age do so in great part because they have genetic variations that affect the basic mechanisms of ageing and result in a uniform decreased susceptibility to age-associated diseases.[62] Our studies and those of others researching the oldest old have proposed that persons who achieve extreme old age probably lack many of the variations (the 'disease genes') that substantially increase risk for premature death by predisposing persons to various fatal diseases, both age-associated and non-age-associated.[63] Recently however, both the New England Centenarian Study[64] and the Leiden Longevity Study[65] noted that the extreme old have just as many disease-associated genetic variants as younger subjects. Both groups hypothesize that other genetic variations (so called 'longevity enabling genes') might confer protection against such deleterious variants and also other factors that would otherwise decrease the 'risk' for exceptional longevity.[66]

The elevated relative survival probability values found among the siblings of centenarians support the utility of performing genetic studies to determine what genetic region or regions and ultimately what genetic variations centenarians and their siblings have in common that confer their survival advantage.[67] Centenarian sibships from the New England Centenarian Study were included in a genome-wide sibling-pair study of 308 persons belonging to 137 families with exceptional longevity. According to non-parametric analysis, significant evidence for linkage was noted for a locus on chromosome 4 at D4S1564 with an Maximum LOD Score (MLS) of 3.65 ($p = 0.044$).[68] A detailed haplotype map was created of the chromosome 4 locus that extended over 12 million base pairs and involved the genotyping of over 2000 single-nucleotide polymorphism (SNP) markers in 700 centenarians and 700 controls. The study identified a haplotype, approximating the gene microsomal transfer protein (MTP).[69] All known SNPs for MTP and its promoter were genotyped in 200 centenarians and 200 controls (young individuals). After haplotype reconstruction of the area was completed, a single haplotype, which was under-represented in the long-lived individuals, accounted for the majority of the statistical distortion at the locus (~15% among the subjects versus 23% in the controls). MTP is a rate-limiting step in lipoprotein synthesis and may affect longevity by subtly modulating this pathway. Given that cardiovascular disease is significantly delayed among the offspring of centenarians and that 88% of centenarians either delay or escape cardiovascular disease and stroke beyond the age of 80 years, it makes sense that the frequency of genetic polymorphisms that play a role in the risk for such diseases would be differentiated between centenarians and the general population.[27,53]

Nir Barzilai and his colleagues, studying Ashkenazi Jewish centenarians and their families, found another cardiovascular pathway and gene that is differentiated between centenarians and controls.[57] In Barzilai *et al*.'s study, controls are the spouses of the centenarians' children. They noted that HDL and LDL particle sizes were significantly larger among the centenarians and their offspring and the particle size also differentiated between subjects with and without cardiovascular disease, hypertension and metabolic syndrome. In a candidate gene approach, they then searched the literature for genes that impact upon HDL and LDL particle size, and hepatic lipase and cholesteryl ester transfer protein (CETP) emerged as

candidates. Comparing centenarians and their offspring against controls, one variation of CETP was noted to be significantly increased among those with or predisposed for exceptional longevity. Of additional note, a number of groups have observed an association between FOXO3A plus or minus FOXO1A and longevity.[70–75] FOXO3A emerged as a candidate gene for further investigation in centenarian association studies because of findings in lower organism studies that noted a role for FOXO in the insulin signalling pathway and ultimately longevity. As with CETP, the question remains of whether these variants are associated with age-related diseases (e.g. heart disease or diabetes) and/or determinants of human ageing itself.

A proposed multifactorial model for exceptional longevity and exceptional survival phenotypes

The fact that siblings of centenarians maintain half the mortality risk of their birth cohort from age 20 years to extreme age suggests that multiple factors contribute to achieving exceptional longevity. For example, sociodemographic advantages may play key roles at younger ages, whereas genetic advantages may distinguish the ability to go from old age to extreme old age. Undoubtedly, exceptional longevity is much more complicated, with temporally overlapping roles for major genes and polygenic, environmental and stochastic components. Such a scenario would be consistent with a threshold model, where predisposition for the exceptional longevity trait can be measured on a quantitative scale. Figure 134.2 illustrates the standard threshold model proposed by Falconer,[76] where it is predicted that the proportion of affected relatives will be highest among the most severely affected individuals. In the case of exceptional longevity, perhaps severity can be measured by additional years beyond a certain age (threshold) or by additional years of delay in age at onset for disease.

Examples of phenotypes fitting the threshold model are early-onset breast cancer and Alzheimer's disease, where relatives of patients who develop these diseases at unusually young ages are themselves at increased risk or liability. Thus, a 108-year-old's 'liability' or predisposition for exceptional longevity is further beyond the threshold than someone more mildly affected, as for example a person who died at age 99 years. One interpretation of data indicating the higher relative survival probability of male siblings of centenarians compared with female siblings is that the males carry a higher liability for the trait, given the presence of the requisite traits. The model predicts that if a multifactorial trait is more frequent in one gender (as is the case with exceptional longevity, which is predominantly represented by females), the liability will be higher for relatives of the less 'susceptible' gender (males, in the case of exceptional longevity).[77] Although we have not yet looked at the relative survival probability of siblings of male versus female probands (something that certainly needs to be done), these elevated risks for male versus female siblings are interesting in this context. The model also predicts that the risk for exceptional longevity will be sharply lower for second-degree relatives compared with first-degree relatives, another observation that we hope to test by having access to many expanded pedigrees. The ramifications of this model holding true for exceptional longevity (and/or exceptional survival phenotypes) include (1) the older the subject, the better the chances of discovering traits predisposing for exceptional longevity and (2) there are gender-related differences in both relatives and probands in 'liability' for exceptional longevity, given the presence of specific traits conducive to exceptional longevity.

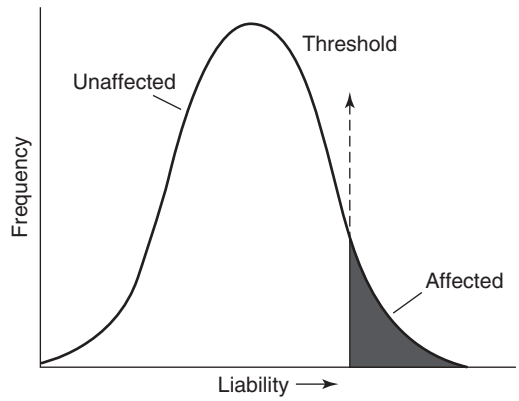

Figure 134.2 Threshold model of a multifactorial trait.

Conclusion

Although centenarians are rare, one per 5000 people in industrialized societies, they are also the fastest growing age category of our population. It is unlikely that they are rare because of any one rare factor. Rather, becoming a centenarian might entail achieving the right combination of genetic and environmental factors, much like winning the lottery requires the right combination of numbers. Each number by itself is not rare, but the right combination of five or six numbers certainly is. Complicating matters, the right combination of factors also likely varies from one person to the next, although there are similarities within families. One reason why the incidence of centenarians is growing may be understood by considering the analogy where the selection of lottery numbers is left less and less to chance. Better health-related behaviours and more effective public health and medical interventions make it significantly more likely for people to reach older age and for some to achieve extreme old age.

With the power of demographic selection, centenarians have already proven helpful in deciphering some polymorphisms and genetic loci associated, positively or

negatively, with exceptional old age. The offspring of centenarians, who seem to be following closely in their parents' footsteps, might yield additional discoveries about phenotypic and genetic correlates of successful ageing. Discovering genes that could impart the ability to live to old age while compressing the period of disability towards the end of life should yield important insight into how the ageing process increases susceptibility to diseases associated with ageing and how this susceptibility might be modulated.[18,38] We anticipate that human longevity-enabling genes will be found to influence ageing at its most basic levels, thus affecting a broad spectrum of genetic and cellular pathways in a synchronous manner. Another approach that researchers are in the early stages of understanding is differential gene expression in models known to slow the ageing process, such as caloric restriction.[78] This may be another tool for discovering longevity-enabling genes. The centenarian genome should also be an efficient tool for ferreting out disease genes. Comparison of SNP frequencies implicated in diseases in centenarians and in persons with the diseases should show clinically relevant polymorphisms. The hope, of course, is that these approaches to gene discoveries will help identify drug targets and create drugs that would allow persons to become more 'centenarian-like' by maximizing the period of their lives spent in good health.

Key points

- An optimistic view. Centenarians support the observation 'the older you get, the healthier you've been'.
- Compression of morbidity versus disability. Achieving exceptional old age likely requires a compression of disability, not necessarily morbidity, towards the relative end of life.
- Nature versus nurture. The majority of the variation in average life expectancy is likely related to health-related behaviours. However, there appears to be a strong familial component to exceptional longevity and, for truly extreme old ages, such as >103 years, specific genetic variations may play a prominent role.
- Centenarian offspring. Following in the footsteps of their parents, the offspring of centenarians are a valuable model for the study of environmental and genetic factors related to successful ageing.
- Genetic findings. Reproducible genetic associations with exceptional longevity are still rare, reflecting the likely complex nature of gene–gene and gene–environment interactions that dictate the ability to survive to extreme old age.

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CHAPTER 135

End-of-life and palliative care

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Introduction

Palliative care (also known as supportive care) encompasses the assessment and treatment of pain and other non-pain symptoms with the goal of relieving suffering across multiple domains. Palliative care can be provided in conjunction with curative treatment at any point in a disease trajectory, even from the time of diagnosis (see Figure 135.1).

Palliative care assists increasing numbers of people with chronic, debilitating and life-limiting illnesses. A growing number of programmes provide this care in a variety of settings: hospitals, outpatient settings, community programmes within home health organizations and hospices. Within these settings, dedicated teams may include physicians, nurses, social workers, chaplains, counsellors, nursing assistants, rehabilitation specialists, speech and language pathologists and other healthcare professionals. These providers assess and treat pain along with other non-pain symptoms and also facilitate patient-centred communication and decision-making. The ideal palliative care delivery system fosters the coordination of continuity of care across settings throughout the disease continuum (see Figure 135.1). Whereas palliative care refers to an approach to care focused on symptom management and improving quality of life, palliative medicine refers to the medical specialty focused on providing palliative care. Despite the emergence of palliative medicine as a formally recognized medical specialty across the world, all physicians who care for patients with serious and advanced illnesses need to be able to provide appropriate pain and symptom management and identify and treat other sources of suffering in their patients. In order to achieve this goal, all physicians need training in palliative care.[1–3]

Palliative care services and palliative care domains are summarized in Tables 135.1 and 135.2, respectivly.

Palliative and hospice care

Palliative care is not synonymous with hospice care in that hospice utilization in the USA requires that a physician endorse a prognosis of 6 months or less in order for a patient to qualify for services. Enrolment in a hospice programme is but a final piece in what the whole of palliative care provides, ideally from the onset of serious life-threatening illness. The goal of palliative care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies. Palliative care is both a philosophy of care and an organized, highly structured system for delivering care. The fundamental elements of hospice and palliative care maintain the following:[4]

1 Pain and symptom control, psychosocial distress, spiritual issues and practical needs are systematically addressed with the patient and family throughout the continuum of care. If present, any conditions are treated based upon current evidence and with consideration of cultural aspects of care.

2 Patients and families acquire ongoing information in a culturally sensitive, appropriate and understandable manner to facilitate the comprehension of the condition and realistic potential of treatment options. In the process, values, preferences, goals and beliefs are elicited over time. The benefits and burdens of treatment are regularly reassessed and the decision-making process about the care plan is sensitive to changes in the patient's condition.

3 Genuine coordination of care across settings is ensured through regular and high-quality communication between providers at times of transition or changing needs and through effective continuity of care and case management.

4 Both patient and family, however defined by the patient, are appropriately prepared for the dying process and for death when it is anticipated. Hospice options are

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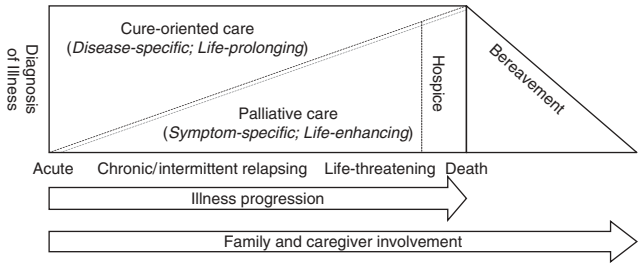

Figure 135.1 Palliative care is most effective for patients and their families when it is integrated across the healthcare continuum. It is optimally initiated in collaboration during the cure-oriented phase, continuing through the course of illness and culminating in end-of-life care (hospice), then bereavement support for family and caregivers. As the disease progresses, more palliative services are integrated into the patient's care as needed. Simultaneously, the emphasis on curative (or life-prolonging) therapies diminishes as the goals of care focus more on palliative care measures (quality-of-life-enhancing).

Table 135.1 Palliative care services.

- Provides relief from pain and other distressing symptoms
- Will enhance quality of life and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy
- Includes those investigations needed to understand and manage distressing clinical complications better
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor to postpone death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated

Source: information from WHO's *Definition of Palliative Care*, http://www.who.int/cancer/palliative/definition/en/(last accessed 26 November 2011).

explored, opportunities for personal growth are enhanced and bereavement support is available for the family.

Symptom assessment and treatment

Palliative care aims at the relief of suffering caused by physical, psychosocial and spiritual aspects of disease and utilizes an interdisciplinary team to provide care. By focused symptom management and clear goals of care, patients living with advanced illness can improve quality of life and spend valuable time with friends, family and loved ones. One of the core principles of the delivery of end-of-life care is the alleviation of pain and other physical and psychological symptoms. The goal of pain and symptom management is a reduction of the symptoms to a level that the patient defines as satisfactory. Providers should be careful not to state that all symptoms will be completely alleviated, because although this goal is sometimes achievable, more often symptoms, such as pain and nausea, are attenuated to an acceptable level.

Pain

The optimal control of pain in the palliative care patient relies on the understanding of the underlying pathophysiology and mechanisms involved and include somatic, neuropathic and visceral aetiologies. These might include tumour invasion of local tissues or metastatic bone pain (somatic), nerve compression or chemotherapy-related nerve pain (neuropathy) or bowel obstruction (visceral). Therefore, management starts with the evaluation of the causes of the pain by a comprehensive history, physical and directed imaging as indicated by the initial evaluation.[5] Many cases of advanced life-threatening illness require the use of opioids; providers should prescribe opioids in doses sufficient to relieve pain and to acquire skills in the management of predictable opioid side effects. Providers must also anticipate and correct patients' misconceptions about the use of opioids, including side effects, addiction, somnolence and hastening of death. Because patients may become unable to take medications orally, the sublingual, transdermal, rectal and subcutaneous routes may be used. The World Health Organization (WHO) pain relief ladder (see Figure 135.2) is a well-established and reasonable starting point in the management of pain symptoms. If pain occurs, the first step is oral administration of medication in the following order: non-opioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient's pain is attenuated. It should be noted that this approach has potential limitations in the context of longer survival and increasing disease complexity if used in isolation and without a comprehensive clinical approach to the pain syndrome. To complement this, combination and adjuvant therapies, including procedural interventions, are used where appropriate, tailored to the needs of an individual with the goals of optimizing pain relief and minimizing adverse effects.[6,7] Furthermore, older and debilitated patients' ability to request 'on demand' (or PRN) medications should compel the provider to consider scheduled dosing, particularly if in a setting such as a long-term care facility where frequent and timely reassessment of pain can be limited by staffing. To maintain freedom from pain, drugs should be given 'by the clock', that is, every 2–6 h, rather than 'on demand'. This three-step approach of administering the right drug in the right dose

Table 135.2 Palliative care domains.

Area	Examples
Physical	Pain, shortness of breath, nausea, fatigue, weakness, anorexia, insomnia, confusion, constipation, treatment side effects, functional capacities, treatment efficacy and alternatives (and patient and family preferences)
Psychological/ psychiatric	Anxiety, depression, care-giving needs or capacity of family; stress; grief and bereavement risks for the patient and family (e.g. depression and co-morbid complications); coping strategies
Social	Family structure and geographic location; cultural concerns and needs; finances; sexuality; living arrangements; caregiver availability; access to transportation; access to prescription and over-the-counter medicines
Spiritual/religious/ existential	Spiritual background, beliefs and practices of the patient and family; hopes and fears; life completion tasks; wishes regarding care setting for death

Source: information from National Consensus Project for Quality Palliative Care, *Clinical Practice Guidelines for Quality Palliative Care*, 2nd edn, 2009, http://www.nationalconsensusproject.org (last accessed 7 November 2011).

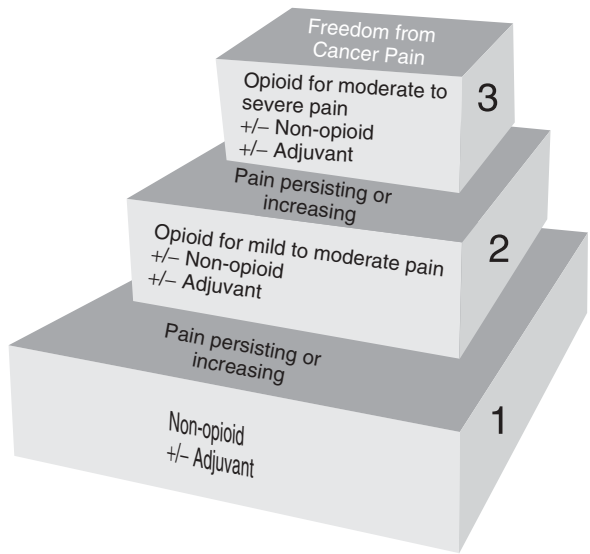

Figure 135.2 *WHO's Pain Ladder*.[8] Reproduced with permission from the World Health Organization from http://www.who.int/cancer/palliative/painladder/en/index.html (last accessed 26 September 2011).

at the right time is inexpensive and 80–90% effective.[8] Surgical intervention on appropriate nerves may provide further pain relief if drugs are not wholly effective (see Figure 135.2).

In essence, the optimal means of providing palliation of pain symptoms is first to consider evaluation and treatment of the underlying removal or minimization of the cause (i.e. disease-directed therapies). For example, in malignant bone pain, surgery, chemotherapy, radiotherapy, and/or bisphosphonates may be used.[9] In infection, antimicrobials or surgical drainage of an abscess may be required. Alongside disease-directed therapy, there are a host of pharmacological and non-pharmacological therapies, which should be used on an individual basis depending on the clinical situation.

Non-pain symptoms

Dyspnoea and respiratory symptoms

Changes in respiratory patterns are common in dying patients. Breathing usually becomes shallow as death nears and periods of apnoea are common. Opioids are the main therapy for treating dyspnoea. Some patients and providers may not be familiar with using opioids for this purpose and should be educated. Secretions that accumulate in the pharynx due to the patient being too weak or unresponsive to swallow or cough can produce a rattling sound that can be distressing to the family. Deep suctioning should be avoided as it can lead to gagging and may be uncomfortable. Atropine, scopolamine or glycopyrrolate (the last does not cross the blood–brain barrier, thereby minimizing contribution to delirium) can be effective in reducing rattle by decreasing the amount of mucus and saliva produced. Rooms should be cool and well ventilated and a fan can aid in reducing the sensation of dyspnoea. It may be appropriate to stop taking blood pressure and monitor only respiratory rate and pulse in order to avoid disturbing the patient or causing alarm to the patient's loved ones.

Gastrointestinal symptoms: nausea and vomiting

Nausea and vomiting are common symptoms in patients with advanced illnesses, including cancer, congestive heart failure, end-stage renal disease and AIDS. For patients and families facing a life-threatening illness, nausea and vomiting can cause substantial distress due to concerns about maintaining adequate nutrition and also fear that these symptoms indicate disease progression.[10] Nausea and vomiting can be triggered by activation of any of four general pathways (Table 135.3).[11]

Each of these four pathways can then activate the vomiting centre, a specific area of the medulla that coordinates the final act of vomiting via the parasympathetic system and gastrointestinal tract. Activation of the vomiting centre is believed to be mediated by histamine (H1) receptors or

Table 135.3 General pathways that can trigger nausea and vomiting.

Area	Activated by	Mediated by
Cortex	Meningeal irritation Increased intracranial pressure Cognitive/emotional factors	Anxiety
Chemoreceptor trigger zone (located in the floor of the fourth ventricle and lacks a blood–brain barrier)	Metabolic abnormalities Toxins Medications	Primarily by the dopamine (D2) receptor, but others include neurokinin-1 (NK1) and serotonin (5HT3)
Vestibular system	Motion or inner ear disease	Via histamine (H1) and muscarinic acetylcholine (ACh) receptors
Peripheral pathways. Signals transmitted along afferent tracts (vagus, glossopharyngeal, splanchnic and sympathetic nerves)	Mechanoreceptors and chemoreceptors in the gastrointestinal tract and heart	5HT3 receptors in the gastrointestinal tract

muscarinic acetylcholine (ACh) receptors.[11,12] Evaluation should include a thorough history and physical examination, with careful attention to common causes of nausea in the terminally ill, including medications (chemotherapy, opioids), constipation, bowel obstruction, electrolyte abnormalities, liver and kidney failure, radiation therapy, CNS lesions and anxiety. Providers should identify the likely mechanism or pathway responsible for a patient's nausea, as this will guide the therapeutic approach.

Non-pharmacological strategies can be helpful for many patients. Patients should eat small, frequent meals as they are able and may need to adjust the types of foods that they eat. Relaxation techniques may be useful for patients with significant anxiety or anticipatory nausea, which occurs prior to chemotherapy sessions due to a conditioned response. Patients with chemotherapy-induced symptoms may consider acupuncture as studies have found that acupuncture-point stimulation appears to reduce the incidence of acute chemotherapy-induced vomiting.[13]

Most patients with nausea or vomiting will need pharmacological therapy. First, determine the clinical aetiology of nausea and select a first-line antiemetic based on the likely mechanism. Then, use the first-line agent on a scheduled basis initially until nausea symptoms are controlled, then consider tapering to as-needed dosing. If symptoms persist, consider adding another agent in a different class while keeping the first-line agent. Nausea is frequently multifactorial and may need therapy directed at multiple sources. Recognize the side effect profiles of different antiemetics and use them to the patient's advantage, not disadvantage (e.g. haloperidol can be useful in patients who also have delirium). Ondansetron causes constipation and would be inappropriate for a patient with nausea due to constipation/obstipation. Finally, avoid using multiple agents in the same class simultaneously (e.g. metoclopramide and prochlorperazine should not be used simultaneously).

Constipation

Constipation is defined as decreased frequency of bowel movements (generally less than three bowel movements per week), hard stool consistency and difficulty with passage of bowel movements.[14] Despite attempts by physicians to describe the characteristics of constipation, there is still a high degree of observer variability in what are considered 'troubling' bowel habits.[15] Ultimately, individual patients' concerns should govern treatment goals for constipation. The strategies for treating constipation are varied and prone to personal preferences of both the patient and the physician;[15] unfortunately, little evidence exists to support rationally choosing any one medication over another.[15,16]

Constipation is a common symptom in chronic disease and can occur from medication used to treat the disease, the debility induced by the disease and the disease itself. The main strategy for treating constipation is prevention. Similarly to other symptom management strategies, chronic use of medications to decrease occurrence combined with strategies to overcome 'breakthrough' symptoms is necessary. The need for rescue medications or laxatives should be anticipated by healthcare providers and included in the care plan.[17] Generally, medications used to treat constipation are divided based on mechanism of action into the following four categories: stimulant laxatives, osmotic laxatives, stool softeners and bulking agents. Combinations of medications with different mechanisms of action are often used to achieve desired bowel function. Stimulant laxatives such as senna and osmotic laxatives such as sorbitol, lactulose and polyethylene glycol are the most common agents. Stool softeners, such as docusate, when used alone are less effective when bowel stimulation is the most likely

underlying aetiology for constipation.[18]. Bulking agents, such as psyllium, used in the absence of adequate oral fluid intake can lead to impaction and should not be used in patients at the end of life.

Bowel obstruction

Bowel obstruction in palliative medicine tends to be as a result of malignancy or its treatments, which include surgical, opioid-related impaction or other sources of inflammatory bowel disease. The obstruction can lead to full bowel obstruction with obstipation or partial obstruction with episodic signs and symptoms. These symptoms usually develop over time and, if accompanied by large-volume emesis, tend to be of the upper gastrointestinal tract. With a limited life expectancy, should aggressive medical interventions fail to relieve symptoms, then endoscopic stenting should be considered if available, as it is potentially less invasive and complicating than surgical intervention. If neither of these options is available or feasible, the use of steroids in conjunction with octreotide to decrease secretions is effective.

Agitation and delirium

Agitation, although not common at end of life, is not infrequent and is troubling for patients and families. If the patient is experiencing agitation due to increased pain, pain should be treated with opioids as appropriate, or if thought to be due to dyspnoea, treated with oxygen and opioids. Behavioural interventions such as brushing a patient's hair or providing music therapy can be highly effective in treating agitation. When these measures do not work and the cause is uncertain, agitation should be treated with low doses of neuroleptics, such as haloperidol (or, if more sedation is needed, chlorpromazine). In palliative care, many drugs used for symptom management can cause neuropsychiatric side effects, as they either directly or indirectly affect the central nervous system. If unrecognized, these effects can generate considerable suffering and iatrogenic harm to patients. Side effects of commonly used palliative care medications include delirium, drug-induced parkinsonism, akathisia, serotonin syndrome and neuroleptic malignant syndrome. Antiemetics such as metoclopramide and haloperidol can cause significant levels of neuropsychiatric toxicity and should be carefully monitored and discontinued if necessary. Many drugs induce delirium, including anxiolytics, opioids, antidepressants, antihistamines, steroids, antipsychotics and antibiotics (fluoroquinolones such as ciprofloxacin). Timing of administration of medications can help determine the offending agent. If the offending medication or medications remain necessary to treat other distressing symptoms such as pain, management of delirium with neuroleptics, opioid rotation and hydration may be helpful.

Fatigue

Fatigue is described as a persistent sense of tiredness or diminished energy related to an underlying life-threatening illness (such as cancer) and/or its treatment, which is not relieved by rest and which causes diminution in functional capacity and quality of life. The treatment of fatigue in patients with chronic illness starts with a review of associated symptoms as many common physical and psychological symptoms are associated with fatigue.[19] Adequate treatment of pain, insomnia or depression is necessary as the common medications used to treat fatigue will not appropriately control these symptoms, other than antidepressant medications. A complete evaluation of possible medication side effects for fatigue inducing medications is also necessary.

After attempts to control other associated symptoms, the commonly used medication classes are psychostimulants, antidepressants, glucocorticoids and haematopoietic growth factors.[20] These medications are used to treat physical exhaustion, depressive symptoms and pathophysiological processes associated with fatigue. Unfortunately, little strong evidence exists to support choosing one class of medications over another and often there is even a significant response to placebo in trials.[21] Given the unclear benefit from one class to another, methylphenidate is the first choice of therapy and can be considered as initial therapy in geriatric patient populations while monitoring for potential side effects.[22,23] Outcomes have been demonstrated in particular patient populations, such as cancer patients,[20,24,25] but its effectiveness has also been shown in smaller trials in a variety of medical illnesses.[22] Other medication classes are limited to specific clinical circumstances, such as the use of glucocorticoids in the prevention of chemotherapy-related fatigue,[26,27] by concern over serious adverse events such as haematopoietic growth factors or by lack of evidence of their effectiveness for isolated fatigue in placebo-controlled trials, such as antidepressants.[28,29] As with any pharmacological intervention, the main guiding principle should be close monitoring to make certain that the therapy is not causing more problems than the symptom, particularly when treating geriatric patients.

Communication

A key element of palliative care is effective communication in order to elicit a patient's preferences and goals of care.[30] Understanding the needs and goals of the patient and family is essential for providing high-quality palliative care. Palliative care teams provide coordination of care and create plans to deal with potential crises, thereby allowing the patient to remain in their setting of choice. Palliative care providers also need good prognostication skills in order to help patients and families define goals of care and make appropriate decisions and plans.[31,32] For example, when

a family calls and states that a patient is eating poorly, it is important to know whether this represents a potentially reversible condition that could be relieved with a treatment or procedure or alternatively is a sign that the patient is approaching the final days to weeks of life. Prognostic information is important in helping patients make treatment decisions. For example, one patient may want treatment order to be able to eat and drink and survive to attend a granddaughter's marriage, while a different patient in a similar clinical situation may decide that they do not want to undergo yet another procedure. When the disease progresses, communication becomes even more important, to ensure that all involved have the same understanding of the prognosis and plan of care. Finally, clinician recognition of the signs and symptoms of the active dying phase of illness is crucial to completing the developmental tasks of the end of life, helping patients and families understand what is happening and what to expect and coordinating care and logistics in the days leading up to death. Although it is impossible to know exactly what will happen to any particular patient, providers can use scored instruments such as the Palliative Performance Scale, Karnofsky, Eastern Cooperative Oncology Group (ECOG) and clinical experience to offer patients and families estimates such as hours to days, days to weeks, weeks to months and months to a year that communicate prognosis while recognizing the inherent uncertainty of such predictions.

Palliative medicine teams formulate and document care plans based on patient wishes, then convey them to patients, family and other providers.[33] Care plans change according to the needs of the patient and family and should involve additional input from other specialists. Functional and cognitive status, disease trajectory, cultural and spiritual preferences and home support must be considered in formulating care plans. For example, a patient may want to remain at home during the final days and weeks of his life, but his wife, who is the primary caregiver, has trouble managing his medications due to mild cognitive impairment. In this situation, home nursing services or hospice can provide a weekly mediset and provide daily telephone call reminders to the wife to ensure administration of the medicines. As death nears, the team may address the possibility of pursuing an inpatient hospice given the wife's limitations.

Psychosocial and spiritual domains

In addition to addressing physical aspects of care, palliative care should address psychological issues and psychiatric needs and support emotional growth.[34,35] Physicians should acknowledge the stress involved in caring for patients with life-threatening illness for both our colleagues and for our patient's family and other caregivers. Caregivers reporting emotional stress have a significantly increased mortality rate; physician identification of vulnerable caregivers and referral to social workers and other community resources can be lifesaving. Physicians must recognize the importance of the time after referral to hospice and understand that patients and families are particularly vulnerable to feeling abandoned at this time by their physicians. Making follow-up appointments for patients and calling on the telephone can help reassure patients that a referral to hospice is not abandonment by the physician. It is important to express thanks and appreciation for the privilege of caring for the patient and, when appropriate, to say goodbye to the patient and their family members. Physicians must also be aware of normal and complicated grief and screen and address those issues appropriately.[36,37] Hospice programmes provide bereavement services and follow-up for 12 months after the death of the patient. Finally, all providers can discuss and offer coping strategies to determine the most constructive approach to dealing with loss based on individual family needs and temperament. Referral to a palliative care social worker can promote access to services, community resources and volunteers that can help patient and family in the home or with transportation. Collaboration with pharmacists can ensure that patients have access to necessary medications; home nursing agencies can ensure that proper equipment is available. Family structure and living arrangements, geographic location, finances and caregiver availability are considered and reflected in the care plan. For example, an older patient with advanced illness may have a partner who is ill and unable to provide care. In such a situation, where the support system is already at its limit, the palliative care team must develop a plan to ensure appropriate care and safety for the patient and their partner.

Sending a patient home without adequate support can often lead to readmission; addressing needs early and activating community support can allow patients to remain at home as long as possible. Different teams may provide these services in differing ways. Some teams have dedicated social workers to address these issues, whereas others may use case managers or nurses to focus on these matters. It is important to realize that the care coordination involved is more than a physician or nurse or social worker can do alone; the interdisciplinary nature of palliative care draws upon the strengths of each field.

Beliefs surrounding illness and death are profoundly influenced by a patient's and family's religious and spiritual values.[38] The salient spiritual needs of patients at the end of life encompass questions of meaning, value and relationship. Physicians can play a key role in helping patients express these needs by asking patients about their religious and spiritual beliefs and practices and how these impact on the patient's view of illness. At a minimum, physicians should recognize these spiritual needs, enquire as to the

patient's spiritual roots and offer a referral to the hospital chaplain. Chaplains and other members of the spiritual care service can address such issues in a non-threatening and supportive way and help facilitate religious or spiritual rituals in addition to contacting spiritual communities identified by the patient and family. When religious beliefs appear to be a barrier to providing good end-of-life care, spiritual engagement is the direct approach to resolution. For example, one patient and his family had a strong religious belief in a miraculous cure for metastatic cancer. The palliative care team chaplain explored this belief explicitly and negotiated a treatment plan that was respectful of the family's belief but also realistic and practical. The chaplain articulated that forgoing additional chemotherapy would not change whether or not a miracle was possible. The patient then accepted a referral to hospice care, where he received continued spiritual, emotional and physical support.

Cross-cultural issues

The experience of a serious illness is deeply affected by a patient's and family's cultural values.[39] Culture often defines how patients and families understand illness, suffering and dying. Encounters between physicians and patients of different backgrounds are common given the diversity in the USA and therefore there are many opportunities for cross-cultural misunderstandings.[40] Use of life-prolonging therapies and technology, the locus of decision-making and truth telling are all influenced by cultural norms. While autonomy is the legal basis for medical decision-making in the USA, some cultures prefer that families make medical decisions as a unit. Adult children commonly wish to protect their parent from bad news and may ask the clinician not to tell the truth. Palliative medicine providers often address this issue by helping the family understand that the information will not be imposed but offered only if the patient indicates an explicit desire to know. Asking the patient if they are the kind of person who prefers all the details about their illness or if they would rather hear a general outline or leave the details of decision-making to a family member does this. Such communication can demonstrate respect for the patient's culture without assuming that the patient will conform to their cultural norms. Skilled communication, genuine curiosity and openness to differences can increase the likelihood that patients and families are satisfied with the process and outcomes of care.

Care transitions in end-of-life care

Healthcare organizations are beginning to use palliative care to improve quality, because it is an effective approach to reducing symptoms and improving patient and family satisfaction. In addition, use of palliative care services can improve transitions of care, support timely and successful discharge, avert unnecessary readmissions and contribute to the efficient use of healthcare resources. Care should be provided in the setting that the patient chooses. If it is not possible to provide care in the patient's preferred location, the least restrictive alternative setting should provide flexible visiting hours, adequate space for visitors and sufficient respite for care providers. When the patient cannot be in their choice of setting, creative measures are taken to make the alternative care setting as comfortable and familiar as possible. Prior to discharge from a hospice, evaluation of home safety and equipment needs is required. Necessary supplies including hospital beds, oxygen, commodes and shower chairs should be delivered prior to patient arrival and the hospital team must ensure that a family member or friend is at the home to accept delivery. If the patient requires ambulance transport home, the timing of arrival should be carefully considered (e.g.. time the ambulance to arrive when young children are at school). Most transport companies allow a family member to travel with the patient if going home from a hospice. For opioid prescriptions, the hospital team should confirm who will prescribe opioids for patient after discharge and verify that the patient's pharmacy actually carries the medication. For opioids, a quantity must be specified (e.g. one cannot write 'one month's supply'). Patients on opioids should not be discharged until the prescription is filled and available at home, as it is often difficult to find a pharmacy that carries these medicines, particularly in poor neighbourhoods. Prior authorization from insurance companies may be required for some new medications or large quantities, hence this should be discussed prior to discharge. Finally, it is prudent to discuss prognosis (hours to days, days to weeks and weeks to months) with patient and family. Some patients and families may opt to attempt to have their loved one get home prior to death, even if death is imminent. Other families may choose to remain in the hospital when death is imminent. Families should be guided in the important developmental tasks of this stage of life, including conduct of important conversations while the patient is still able to participate. Many teams provide family members with a written list of Byock's 'Five Things' to think through and discuss as applicable when a loved one is dying: thank you; forgive me; I forgive you; I love you: goodbye. Depending upon their age and wishes, children may visit after preparation for what they will see and encouragement to draw a picture or write a letter to the patient expressing their feelings towards them, as a means of saying goodbye.

Key points

- Palliative care encompasses the assessment and treatment of symptoms with the goal of relieving suffering across multiple domains.

- The ideal palliative care delivery system fosters the coordination of continuity of care across settings throughout the disease continuum.
- The goal of palliative medicine providers in the process of providing symptom management is to alleviate suffering regardless of its cause.
- The optimal control of pain in palliative care requires an understanding of the underlying pathophysiology and mechanisms involved and include somatic, neuropathic and visceral aetiologies.
- Understanding the multidimensional needs and goals of the patient and family is essential in providing high-quality palliative care.
- Use of palliative care services can improve transitions of care, support timely and successful discharge, avert unnecessary readmissions and contribute to efficient use of healthcare resources.

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CHAPTER 136

End-of-life care: special issues

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Palliative care

The World Health Organization defines palliative care as an approach that 'improves the quality of life of patients and families who face life-threatening illness, by providing pain and symptom relief, spiritual and psychosocial support'.[1] The National Institute for Health and Clinical Excellence (NICE) states that 'patients want to be treated as individuals, with dignity and respect, and to have their voices heard in decisions about treatment and care. Should they need it, they expect to be offered optimal symptom control and psychological, social and spiritual support. They want to be assured that their families and carers will receive support during their illness'.[2]

Most healthcare professionals will at some time during their careers provide care for those who are terminally ill and dying. These professionals will already be providing personalized care with the aim of improving the quality of life of their patients, whether or not the option of life prolongation is available. Those involved in such care will acknowledge the need to relieve psychological distress in addition to physical symptoms and the benefits for the patient of providing support to informal carers. Thus, all healthcare professionals are providing palliative care – sometimes termed 'generic' palliative care – and those providing it should be able to[3]

- Assess the care needs of each patient and their families across the domains of physical, psychological, social, spiritual and information needs.
- Meet those needs within the limits of their knowledge, skills, competence in palliative care.
- Know when to seek advice from or refer to specialist palliative care services.

In addition to the generic palliative care provided by all those with patient contact, specialist palliative care is provided (in some areas of the world) by those who have undergone extensive education and training focusing on the care of patients with terminal illnesses. These specialists will often work exclusively with palliative care patients. Current UK guidance emphasizes the benefits of providing this care by working in multiprofessional teams.[2] The UK's National Council for Palliative Care recommends that 'specialist teams should include palliative medicine consultants and palliative care nurse specialists together with a range of expertise provided by physiotherapists, occupational therapists, dieticians, pharmacists, social workers and those able to give spiritual and psychological support'.[3]

The benefits of a palliative approach

About 1% of the Western population die each year and, although it can be hard to identify those patients who will die, identification of those patients likely to benefit from a palliative approach to their care can improve the experience of the patient and their family at the end of life. Such a palliative approach can help symptom control interventions take priority over those which lengthen life, and also facilitate discussions to inform advance care planning and the provision of care. This approach enables care to be tailored to the needs of the patient, the family and informal carers.

It may be possible to avoid crises and prevent hospital admissions, something that is desirable in view of the fact that studies in the UK reveal that 49–100% of patients with cancer express a wish to be cared for and to die at home,[4] but in 2008 only 26% of cancer deaths and around 20% of all deaths occurred at home.[5,6] More meaningful is the result from an audit in a hospice in England that showed for patients who had a documented preference, the place of death matched the most recently documented preferred place of care in 73%.[7]

Traditionally, cancer patients and those with acquired immune deficiency syndrome (AIDS) have had access to specialist palliative care (SPC) services, whereas those with other terminal diagnoses have tended not to be referred. This may be due, at least in part, to the fact that treatments for cancer and AIDS prolong life at the expense

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of its quality and that hospices were often founded by cancer charities. Another factor favouring implementation of a palliative approach for cancer patients is the prompt to do so provided by the withdrawal of anticancer treatments, when prognosis may still be of the order of weeks to months. In contrast, many interventions for patients with other diagnoses, for example, heart failure and chronic obstructive pulmonary disease, prolong life while at the same time improving symptom control. These treatments are often withdrawn only very shortly before death, (precisely because they provide an element of symptom control) and their withdrawal is therefore not a useful prompt for initiation of a palliative approach.

However, patients with non-malignant terminal diseases have a significant symptom burden[8] and would often benefit from referral to SPC services. Professionals without extensive experience of using symptom control drugs such as opioids, anti-emetics and benzodiazepines are often concerned about their use, particularly about side effects and the potential for harm to the patient. One worry often cited is concern about the sedative and respiratory depressant effect of opioids, especially in frail elderly patients who are likely to have a degree of renal impairment. There is significant evidence that appropriate titration of symptom control drugs (including opioids) does not risk premature death due to sedation and respiratory compromise.[9] There is also much evidence to confirm the beneficial effects of appropriate use of these drugs in these patients, without an excessive burden from side effects.[9,10]

One of the barriers to use of a palliative approach for patients with non-malignant terminal diagnoses is the difficulty in prognosticating for this group of patients. A trajectory of gradual decline in function, punctuated by episodes of acute illness, from which the patient may recover with aggressive treatment, is typical of end-stage chronic obstructive pulmonary disease and heart failure.[11]

For some patients, families and professionals, it can be hard to understand that using a palliative approach to symptom control does not preclude aggressive interventions (including admissions) for acute decompensation. Referral to specialist palliative care teams (SPCTs) can provide a welcome opportunity for discussions about a patient's goals, with clarification of the aims of treatment. Such discussions, if undertaken sensitively and over a period of time, can assist with advance care planning (ACP). Following discussions, patients and families may be empowered to decline admissions in the event of future deteriorations, in preference for treatment in the community. In the absence of these discussions, patients and their relatives are often not aware that there are alternatives to inpatient treatment. In addition, primary care teams may not be aware of how to look after such sick patients in their own homes and may need professional support from the SPCT to show them how to organize care and give them the skills and confidence to offer it.

A third disease trajectory is often demonstrated by patients with advanced dementia and elderly patients with multiple comorbidities.[11] These patients have very low levels of functional ability and suffer from fluctuations in their condition over time. The precipitants for any deterioration may be unclear and may be potentially reversible, for example, a urinary tract infection that can be treated with oral antibiotics. This group of patients can also benefit from ACP (if this is possible) or planning for future care carried out by professionals in collaboration with relatives and informal carers. Use of such a palliative approach for these patients can inform decisions about how far to escalate treatment and give professionals insight into which proposed treatments are really likely to gain the patient any meaningful quality or length of life. These patients are extremely frail and are often cared for in nursing homes or similar facilities.

One of the questions that professionals often fail to consider when a patient's condition deteriorates is, 'Is this patient dying?' Unless this possibility is considered, many of these patients will continue to be removed from their homes and admitted to acute hospitals for their last hours and days of life.

It is therefore clear that many patients with terminal diagnoses would benefit from the use of a palliative approach by their team of healthcare professionals. These benefits include improved symptom control and greater openness about likely prognosis and the aims of medical interventions, which may inform ACP and relieve psychological distress for all involved. Additional benefits of using this approach include provision of support for relatives and informal carers, better coordination of care and tailoring care more closely to the needs of patients and their families.

To help overcome the difficulties of prognosticating for patients with diverse diagnoses, The Gold Standards Framework,[11] developed in England, proposes the use of the following three triggers to identify those patients who would benefit from a palliative approach:[11]

1 The 'surprise' question – Would you be surprised if this patient were to die in the next 6–12 months?

2 Choice/need – The patient with advanced disease makes a *choice* for comfort care only, not 'curative' treatment or is in special *need* of supportive/palliative care.

3 Clinical indicators – Specific indicators of advanced disease for each of the three main end-of-life patient groups as described above.

When to involve SPCTs

One of the questions that those caring for patients with a terminal diagnosis must consider is whether and when to refer to SPC services. Not all patients will benefit from a

referral and many patients can be cared for by their usual doctors and nurses, either in the community or as inpatients. When it is clear to the patient, his relatives and informal carers and his professional carers that he is terminally ill, several factors must be considered to determine whether a referral to SPC services will be of benefit.

For some patients, even when their usual team of healthcare professionals has adopted a palliative approach, there is the potential for further improvements in care with the involvement of SPCTs. Sometimes the SPCT can access sources of care and equipment not available to others. Team members may have the luxury of more time to spend with patients and their families than non-specialists. This time is often needed for the delicate nature of discussions relating to ACP, which often develop over the course of several weeks as the patient assimilates information at their own pace. There is also the potential for relief of psychological distress and the facilitation of more open communication between the patient and their family. SPCT doctors and nurses will be much more familiar with pharmacological interventions for symptom control, will have a greater knowledge of the evidence supporting their prescribing and will be able to recommend the use of drugs in ways that minimize the risks and burdens associated with their use. Thus any terminally ill patients with multiple or severe symptoms are likely to benefit from referral to SPC services.

Referral to specialist services should also be considered if the patient's usual team of professionals is not familiar with managing the terminal phase of the disease in question (for example, the incidence of motor neurone disease in the UK is low, so only neurologists, respiratory physicians and SPCTs care for these patients regularly).

Even when professionals recognize the benefits of a palliative approach, a referral may be hindered by the patient's lack of awareness of their terminal condition and the inability of the referring team to acknowledge openly that disease control has failed. Even when patients and families are aware of this, they may block referral to the SPCT because of (incorrect) beliefs that this indicates that they are in the last weeks and days of life. In such circumstances, the professional team should try to initiate sensitive discussions about likely prognosis and the benefits that may be achieved by engagement with SPC services.

Withholding and withdrawing treatment

One of the most important roles of healthcare professionals in any setting is to make assessments of which interventions are likely to be of benefit to each patient and recognize those which are failing to provide benefit. This skill is a key duty and responsibility of healthcare professionals. When any intervention is considered for a patient, the likelihood and magnitude of benefit that the patient can expect to gain must be balanced against the magnitude and likelihood of potential harms and possible risks to the patient. It is only when greater benefits than harms are expected that it is appropriate to offer an intervention to the patient.[12] Similarly, ongoing interventions should be reassessed routinely and the balance of benefits, burdens and risks considered. For palliative care patients with progressive conditions, these may have altered so that when an intervention ceases to have a net overall benefit for the patient, it should be discontinued. For example, when palliative chemotherapy is offered to a patient with metastatic rectal carcinoma, this is done with the hope that the cancer's growth will be slowed, with consequent benefits in length and/or quality of life for the patient. If, after three cycles of chemotherapy, it becomes clear that the patient's disease is progressing despite the treatment and he or she is now suffering from significant side effects, then chemotherapy should be stopped. Such decisions to withhold or withdraw treatment are morally justifiable because they follow from judgements about beneficence and non-maleficence, and also concerns to ensure distributive justice (if resources are consumed in providing expensive, ineffective and harmful chemotherapy for one patient, they are then not available for the provision of effective treatment for another patient).

Implementing these decisions can be particularly challenging if the patient and/or their family wish to continue the ineffective intervention. Many patients (and indeed clinicians) equate ongoing active treatment with hope and fear the destruction of the patient's emotional wellbeing by its withdrawal. The emotional burden of treatment withdrawal is compounded if the patient is told 'there is nothing more that can be done' and to the clinician this sentiment confirms their failure. In fact, it would be much more accurate if clinicians explained to patients and relatives that (to paraphrase a well-known advertising slogan) 'there is nothing more that I can do, but I know a man who can'! It is at this point, when the clinician feels that there is nothing more that can be done, that SPC services should be involved. The approach of specialist palliative care services is that there is *always* something, however small, that can be done for a patient to improve their quality of life. This may involve drug treatments for symptom control or interventions that are not traditionally within the domain of healthcare, such as facilitating the patient's attendance at a family wedding. The authors argue that the cessation of some treatments (although constituting bad news for the patient) does not mean the loss of all quality of life. Instead, such a decision can provide an opportunity for the patient to revisit their priorities and make plans for the time they have left.

This is not to deny the emotional burden on healthcare professionals of making these decisions and then communicating them to patients and relatives. This emotional burden is greater when decisions are made to withdraw a

treatment that has already been started than when deciding not to offer a treatment in the first place. This may be partly due to the different types of conversation needed when withdrawing a treatment as opposed to withholding it. In the latter case, the patient and relatives may not be aware of the possible treatment and in these circumstances clinicians often do not feel the need to explain that a treatment is being withheld, which of course makes for an easier dialogue from perspective of the emotional burden on the professional. In all cases where an ineffective and unduly burdensome treatment has been withdrawn or withheld, it is the patient's underlying disease that causes their death. However, this is much more apparent to observers when a treatment has never been started. In contrast, when an ineffective treatment is trialled and then withdrawn, the patient's relatives and some of the professional team may believe that death was caused by the lack of treatment. This is a particular risk when the time between treatment withdrawal and death is short, as often happens when ventilatory support is withdrawn from a ventilator-dependent patient. In such cases, conversations with relatives and between team members in advance of treatment withdrawal should focus on the fact that the particular treatment is not providing any useful benefit for the patient and that it is the underlying disease that will ultimately cause death.

The moral argument for the equivalence of withholding and withdrawing ineffective and unduly burdensome treatments has been made in the preceding paragraphs and is supported by UK law.[13] Thus there is no moral or legal pressure to favour withholding treatment over withdrawing it. This enables clinicians to make decisions in the best interests of patients and to undertake a time-limited trial of any intervention whose effectiveness for the patient in question may be in doubt.

Cardiopulmonary resuscitation (CPR)

CPR is a medical treatment which is no different to any others from an ethical perspective. However, decisions to withhold CPR have attracted much controversy over recent years and these decisions warrant further discussion.[14,15] One of the reasons for clinicians' frequent discomfort about making decisions that CPR would be an inappropriate intervention stems from confusion about the two related but distinct ethical decisions that must be made.

The first decision (as with all other medical treatments being considered for a particular patient) concerns the likelihood and magnitude of benefit that the patient can expect to gain from CPR in contrast to the certain harms and likely risks involved. The chance of CPR having any physiological benefit (the return of a pulse with accompanying cardiac output and spontaneous respiration) is markedly decreased in patients with advanced terminal disease (including cancer, end-stage organ failure and degenerative neurological disease).[16] In the unlikely event of such physiological benefit, the chances of it being sustained and the patient gaining any useful quality of life are miniscule; in one series, none of the terminally ill patients who had CPR performed survived.[17] One of the harms associated with unsuccessful CPR is prevention of a peaceful and dignified death, something that most patients and their relatives would wish for.[18] A thorough ethical analysis of these issues will include consideration of the opportunity costs associated with staff attempting to resuscitate a dying patient. We will address the issue of patient autonomy in later paragraphs.

In making a decision about the prospect of success from CPR, the clinical team is not being asked to judge whether the patient's life has value or what the patient's quality of life is. Only the patient themself can decide whether they have sufficient quality of life to warrant attempts to prolong it. If the multiprofessional team have first decided that CPR carries a realistic prospect of physiological success for a particular patient, discussion with the patient will then be required, to ascertain whether they wish to consent to attempts at CPR in the event of a cardiac arrest.[18]

Should clinicians decide that the likelihood of physiological success from CPR is so slight that it is not appropriate to offer this intervention, they must then address the thorny issue of whether and how to communicate this to the patient and their family. As mentioned above, CPR is (from a moral and legal perspective) a medical intervention like any other. Clinicians are not generally obliged to have an explicit discussion with patients about all possible interventions and why they would be ineffective for that patient. Thus there is no requirement (either legal or moral) to inform a patient that a decision not to attempt CPR (DNACPR) has been made.[19,20]

Sensitive enquiries often ascertain that patients would prefer not to receive bad news, and that at least some patients are content with the professional team making this decision without their involvement.[18] Clinical experience informs us that many patients will become unduly distressed by such a conversation. Although it may not be necessary or desirable to tell all patients that a DNACPR decision has been made, this does not remove the responsibility of professionals to attempt to ensure that the patient and their relatives are aware of the terminal nature of their diagnosis and that the focus of care is on comfort and symptom control, rather than prolongation of life. The Preferred Priorities for Care documentation[21] and (for those in the last days of life) the Liverpool Care Pathway for the Dying Patient[22] will prompt professionals to ensure that patients and their relatives understand the aims of care.

Difficulties around communication of DNACPR decisions arise when a healthcare professional is not clear themself about the stages described above for making and communication these decisions. In such circumstances, it is all too easy to initiate a discussion which appears to give the

patient a choice about whether to consent to CPR.[18] These discussions are entirely appropriate when (as considered above) the clinician feels that there is the potential for the patient to benefit from CPR. However, such discussions are not appropriate if the multiprofessional team judges that attempting CPR would be inappropriate for this patient. The patient can be misled into thinking that they have a choice about this intervention and that is has a realistic chance of success and is then upset when they are told that CPR will not be attempted.[18]

One of the reasons why patients and their families may expect CPR (and be upset by a DNACPR decision) is their lack of understanding of what it can achieve. Portrayal of CPR and its success rates in popular medical television dramas show much greater rates of success than actually occur in clinical practice.[23] When patient and relatives are truly aware of the potential harms of CPR, the extremely low chance of meaningful success and understand and accept the terminal nature of their disease, they often concur with a DNACPR decision. The challenge for those clinicians who aspire to an explicit discussion about CPR with all patients is to get the patient to this stage without unnecessary distress – something that it may not be possible to achieve.[18]

Clinicians should also remember that the pathophysiology of death, whether it is expected or sudden, is that of a cardiorespiratory arrest. In inpatient settings and in the community in the UK, the default position is that CPR should be attempted in the absence of a DNACPR decision. This highlights the need for a DNACPR decision to be made and documented for all patients who are expected to die and for whom the aim of care is a peaceful and dignified death.

Artificial nutrition and hydration

Nutrition and hydration needs should be considered separately in clinical decisions. Although people can live for a time with inadequate or almost no nutrition, hydration is essential to maintain life as failing renal function and dehydration can occur rapidly. When a patient cannot swallow oral fluids, maintaining a degree of hydration can be an important comfort measure. A subcutaneous fluid infusion can be set up in almost any environment; it is very simple to administer through a subcutaneous needle in to the abdominal wall, carries a very low risk of any complications and is as effective as intravenous hydration for long-term maintenance.[24] Maintenance of hydration can be an important adjunct to good mouth care, but care must be taken to avoid fluid overload, including in those with cardiac decompensation.

Nutrition is an emotionally charged area. Families often feel an overwhelming desire to try to provide calories, in particular as food, for a person who is dying; dying patients often have no appetite or distorted taste and may have disease-related cachexia. Anorexia can be the first sign of subclinical nausea, so it is important to exclude causes of nausea, such as hypercalcaemia, renal failure and infections, particularly of the urinary tract. In the past, steroids have been advocated as a short-term expedient to stimulate appetite, but their problems are legion. Apart from only having a short-lived effect on appetite, steroids can worsen muscle wasting, precipitate gastrointestinal erosion and bleeding and often have a profoundly disturbing effect on mood.[25] Although a frank steroid psychosis is relatively rare, patients often complain of feeling emotionally labile with impaired sleep. Megestrol acetate appears to have no advantage over glucocorticoids.[26]

Any form of artificial nutrition needs very careful consideration, because in most patients it is unlikely to bring about a benefit either in survival or in quality of life. Nasogastric feeding is very uncomfortable because the tube through the nose is irritating, disfiguring and it carries a significant risk of aspiration pneumonia. Percutaneous endoscopic gastrostomy (PEG) feeding requires a tube to be placed; although this is a relatively simple procedure, it can be most disruptive in someone who is frail; 15% of patients suffer from some side effects such as diarrhoea.[27] Therefore, the patient's informed wishes and the anticipated benefits and potential harms need to be weighed carefully in someone with a short life expectancy, although in the longer term benefit is likely to be seen with PEG feeding.[28]

Care planning

Autonomy

The concept of autonomy is very important in medicine, because it protects patients from interventions to which they do not consent. Autonomy means 'self-governance'; it is our ability to govern ourselves in our daily lives. Respect for autonomy allows each person to be respected as an individual with their own thoughts, wishes, privacy and personal boundaries; it recognizes their relationships with others and the effects of their actions on others. An individual's autonomy is not limitless and should be restricted when it infringes the autonomy of another.

It is a concept that establishes equality in relationships and gives rise to all the principles that underlie consent, particularly that valid consent is informed, voluntary and that the person has the mental capacity (or competence) to make the particular decision.

In care of the elderly, this is precisely why the healthcare professional may be assaulting a person if they assume consent but have ignored the communication needs of the patient. For example, a deaf patient may need a hearing aid in place to be able to understand an explanation; for many elderly people a patient leaflet is no use if the typeface is too small or the patient does not have their reading glasses.

Much of the media refer to autonomy as if it means 'I want therefore I get'. It does not. In a patient with capacity it does mean 'you may not do things to me without my permission' – so even if a patient's refusal of treatment seems unwise but they have capacity, then their refusal stands. In the face of such a decision, the professionals' duty of care does not diminish; all care should continue without prejudice.

In those with reduced capacity, every effort should be made to maximize their capacity for autonomous decision-making before deciding that they are unable to make a decision. At the point that they are deemed to lack capacity for a particular decision, the lead clinician – usually the doctor – must take a decision in the 'best interests' of the patient as a person.

Personhood exists in the patient even in extremis and after losing many functions in life – while still alive they are no less a person even though they may be a different person to the one they were before becoming ill. Once dead, they are no longer a person and have become a corpse, so responsibly for the body falls to the person named as next of kin.

Advance care planning

ACP has recently been adopted in clinical practice as a process of discussing and recording wishes to future care and treatment. Various care planning tools have been developed, but they are no substitute for simple communication with the patient and clear documentation in the clinical record.[29]

Part of the discussion around ACP involves documenting a patient's particular wishes in addition to knowing whether the patient has an advance decision to refuse treatment. Such an advance decision, known as an advance directive in Scotland and colloquially called a living will, is legally binding in UK law provided that it is valid. This means that it must apply to the specific situation being considered, must have been drawn up at a time when the patient had the mental capacity to take such a decision, the decision must have been voluntary and adequately informed and the patient must not have acted to render the advance decision invalid.[30] Whatever is written down, the clinician must check with the patient the nature of their current wishes if the patient has capacity, as advance decisions only come into effect once the patient has lost capacity for making the decisions in question. If the clinician is in doubt over the validity of a documented advance decision and the patient lacks capacity, then the reason why the validity is in doubt must be clearly documented and decision-making reverts to the 'best interests' principle. However, clinicians are still obliged to use the advance decision to inform their best interests decision-making.[30]

Future care planning

Many palliative care patients will not have participated in advance care planning and are not able to be involved in decisions about provision of care. Reasons for this include cognitive impairment, extreme fatigue or preferences for minimal involvement in decision-making. The legal framework outlining the way in which decisions must be made for these patients varies between countries. When making decisions for those without the necessary mental capacity, clinicians must consider what factors should inform their decisions and who should participate in decision-making.

In the UK, there are specific circumstances when decision-making should be undertaken by a proxy previously nominated by the patient. These circumstances are laid out in the relevant legislation. In all other circumstances, decisions should be made by the team of healthcare professionals. In these cases, clinicians should be clear both to themselves and to others that liaison with relatives and informal carers provides valuable information about what might be in the patient's best interests. If relatives are given the (incorrect) impression that decisions about how to proceed are theirs to make, they may suffer significant distress brought about by the emotional burden of decision-making, even if a consensus between different individuals can be reached.

Legislation sets out factors that should inform decisions for patients who lack capacity. In England and Wales, a broad definition of best interests is outlined by the Mental Capacity Act 2005.[31] This encompasses much more than just physical aspects of the patient's care and includes aspects of their psychological wellbeing.

Irrespective of the way in which decisions must be reached, there are benefits for both patients and health services in attempting to make decisions about how and where a patient should be cared for in the future. This is especially true for patients who are expected to die in within weeks to months. We have already cited the example of frail nursing home patients being admitted to hospital for their last hours of life because nobody recognized that they were dying. There is a particularly strong argument to be made for what we shall call 'future care planning' for all nursing home patients. In order to need nursing home care, patients must have a significant disease burden and be sufficiently frail that they need 24 h nursing care. Many of these patients are suffering from one or more progressive conditions which will shorten their life. Many of them will also have a degree of cognitive impairment which is likely to contribute to psychological distress and confusion in the event of a change of environment. In the event of a deterioration in the condition of such a patient, the likelihood of significant gains in quality or length of life from admission to hospital are minimal and the harms and risks are substantial. All healthcare systems have finite resources, so one ought also to consider the opportunity costs of inappropriately

aggressive intervention with minimal chance of gain (with other patients not receiving care from which they may have a greater chance of benefit). Hence there is a strong case for collaborative planning of future care for all nursing home residents, involving medical and nursing staff as well as family members. Decisions can be made that some interventions ought not to be considered for particular patients. This might include any investigation or treatment that required hospital admission, including CPR and ventilation. Some interventions that could be administered in the nursing home may also be deemed inappropriate in the light of an analysis of the likely benefits, burdens and risks involved, for example, artificial nutrition for a patient with advanced dementia, whereas others such as antibiotics for a urinary tract infection may remain appropriate for almost all patients.

Future care planning can also be helpful for palliative care patients in settings other than nursing homes. In places where usual care services are only available during the working week (which in the UK constitutes only 24% of the whole week), patients at home and in hospital are very likely to be reviewed by somebody unfamiliar with their case in the event of a deterioration. Without a clearly documented plan for future care (similar to those described above for nursing home patients), decisions may be made to escalate care inappropriately or to restrict care inappropriately. Although good practice with respect to thorough handover and high-quality case notes will reduce the risks of inappropriate decisions, a time of unexpected crisis is not the time for an unfamiliar nurse or doctor to attempt a complex discussion with a patient and their family about the options for care. It is highly likely that better quality decisions and therefore better outcomes will follow decisions about future care that are made by the patient's usual healthcare team and are subject to regular review.

Terminal care

In earlier parts of this chapter, we have considered patients with terminal diagnoses and prognoses of weeks to months. For many terminally ill patients, there is a period of hours to days when it is clear that they are actually dying – the terminal phase. Not all patients have a recognizable terminal phase; instead, some will die very suddenly, for example following a massive pulmonary embolus or terminal haemorrhage. For those patients who have entered the terminal phase, provision of high-quality evidence-based care can be facilitated by using the approach set out in the Liverpool Care Pathway for the Dying Patient (LCP) (or other similar documentation).[22] Care pathways such as these prompt professionals to review the patient's care thoroughly, to continue or initiate parenteral routes for administration of symptom control drugs, to prescribe in anticipation of the development of likely symptoms and ensure the drugs are available, to discontinue ineffective and burdensome interventions and to address relatives' needs for information and support. Use of the LCP and other similar pathways has been shown to improve symptom control for patients in the terminal phase,[32] improve the quality of communication between professionals and relatives[33] and improve nurses' confidence in caring for the dying.[32]

One of the key factors in ensuring that patients benefit from the use of such a pathway is that an informed and considered decision is made before using it to guide care. As is suggested by the name, use of the Liverpool Care Pathway for the Dying Patient only provides prompts to high-quality care for patients who are actually dying. It is imperative that healthcare teams consider and address (as appropriate) any reversible causes for a patient's deterioration before using the care pathway as a tool to guide care.

It is worth noting that the condition of some patients actually improves when their care is guided by an end-of-life care pathway.[32] If it becomes evident that the patient is no longer dying, use of the care pathway should be discontinued and review of the situation may highlight the need to commence (or recommence) additional interventions. One of the reasons why patients may improve in these circumstances is the cessation of medications not strictly necessary for symptom control; in retrospect, it may be clear that such medications were the cause of a patient's deterioration, rather than the underlying disease process.

Terminal sedation

Sedation at the end of life should rarely be necessary. There are a few situations where sedation to decrease conscious levels may be required as a way of controlling difficult symptoms, such as when a patient is exhausted with complex pain or profoundly distressed following a neurological insult. The use of sedation in this way requires patient consent as it is a therapeutic intervention. In the event of the patient lacking capacity, a short period of sedation, for example to control difficult delirium, may be deemed to be in the patient's best interests; such a decision should only be taken with the agreement of the person legally appointed by the patient to have power of attorney for health and welfare decisions or, failing that, following consultation with the patient's preferred proxy decision-maker and other interested parties. Clinicians should consider and review the likely benefits, burdens and risks of ongoing parenteral hydration and enteral nutrition for patients who require sedation for the relief of intractable symptoms.

Sedation with short-acting agents, such as midazolam, can be achieved by carefully titrating up the dose in increments to achieve the desired therapeutic effect. Regular review is essential, so that the dose can be lowered again at the time agreed and the clinical situation reviewed.

In the last days and hours of life, patients may become restless and appear anxious. Small anxiolytic doses of a short-acting benzodiazepine can be helpful to relieve distress, but it is not necessary deliberately to render the patient deeply unconscious. This principle is set out in end-of-life care pathway documentation, such as the LCP.[22]

A protocol for 'terminal sedation' has been devised in The Netherlands and is used as a way to achieve deep sedation which is maintained until death occurs.[34] In this approach, higher doses of sedative drug are given by continuous infusion and nutrition and hydration withheld. It has been suggested that this approach is linked to euthanasia, without incurring the administrative framework for euthanasia required in The Netherlands.

It is possible to achieve clarity about the difference between palliative sedation and deliberate attempts to end the patient's life by considering the following factors. The aim of palliative sedation is to relieve intractable symptoms; this is achieved by careful titration of sedative medications according to their effect on the patient's symptoms and the patient's death occurs as a result of their underlying disease process. In contrast, administration of sedative and other drugs to render a patient deeply unconscious, without titration according to effect and without considering the possibility of ongoing artificial nutrition and hydration appears to be undertaken with the aim of shortening life and may well have this effect.[35]

Assisted dying

Assisted dying is the euphemistic term widely used to cover assisted suicide and euthanasia. There has been extensive debate about 'assisted dying' in many countries in the world, but at the time of writing, Belgium and Luxembourg have legalized euthanasia, Oregon and Washington states in the USA have legalized assisted suicide and The Netherlands has legalized both.

Assisted suicide is where a person supplies the means to help another take their own life; it may involve the prescription of a lethal dose of a drug (physician-assisted suicide) or may involve the supply of other lethal means by someone who is not associated with healthcare (assisted suicide). Euthanasia is the deliberate giving of a lethal drug to bring about a patient's death as rapidly as possible; in the context of this section, the term euthanasia is used as applying to voluntary euthanasia only.

Arguments in favour of assisted suicide/euthanasia revolve around patient autonomy, existential distress and a sense of futility at enduring the course of a final illness. Arguments against assisted suicide/euthanasia focus on public safety, namely the danger to vulnerable patients of coercion, the inability of safeguards to be watertight and the principles around respect for life.[36]

As with any form of consent to an intervention, proposed safeguards around an application for assisted dying require the patient to be fully informed, making a decision of their own free will and with the mental capacity appropriate to the decision being taken. Difficulties with accurate information arise because diagnosis is an imprecise art; a significant proportion of antemortem diagnoses are shown to be inaccurate at postmortem,[36] so patients who believe their life expectancy to be short or with a catastrophic course may be very wrong. Mental capacity must be intact to take such a momentous decision (that of ending one's own life); it is of note that in an in-depth study of 18 patients receiving a prescription for lethal drugs under the Oregon Death with Dignity Act, three were found to have an unrecognized and untreated depression.[37] Detection of coercion is difficult, particularly when internal coercion (feeling a duty to die) rather than external coercion is present.[36]

The UK Director of Public Prosecutions has indicated that any physician or other healthcare worker is particularly likely to be prosecuted for assisting suicide. His guidance on prosecution for assisting suicide also states that underlying disease or disability of the victim is not a mitigating circumstance when considering whether a person assisting a suicide should be prosecuted.[38] Indeed, the law gives a message about how we behave – it gives a clear and strong message that the routinization of assisted suicide (death by appointment) is not condoned. However, in the event of a person assisting the suicide of another in extremis purely out of compassion, the law will be interpreted with compassion too. The medicalization of assisted suicide is particularly dangerous, as recognized in the Director of Public Prosecutions' guidance, and our suicide prevention strategies in society hold good whatever the age or infirmity the patient may be. The importance of all efforts, however small, being made to improve quality of life is no less important when individuals are incurably ill and dying.

When a patient expresses a wish is for assisted suicide or euthanasia, it is important that the clinician considers what the real question is that the patient is asking. Does the patient have a confirmed wish to die or are they asking whether their life is worth carrying on with? The way in which the clinician responds will have an enormous influence on the way in which the patient perceives the future and any hope for quality of life. It is important to remember that many elderly patients dying today have witnessed poor deaths, often without the benefit of any palliative care intervention at all. Up until about 20 years ago, morphine was rarely used with dying patients, through a mistaken belief that morphine would hasten death. The result was that many patients were left with unrelieved pain and distress – a situation witnessed and living on in the memory of those who were bereaved. These experiences will inevitably colour the perception of death and dying of the elderly person who is now the patient.

Bereavement

The process of grief begins from the time that someone's health is deteriorating. For many elderly couples who have lived together for many years, this also marks the beginning of a very painful parting. For the relative who is not dying, the loss of a lifelong partner is equivalent to part of their own personal dying.

The way in which people adapt in grief is influenced by their experience of being bereaved. It is very important that relatives are aware of what is happening, are encouraged to be involved in care and that their concerns are listened to. Even when frail and elderly, they may want to be at the bedside of the person they love; it does them a great disservice to deny them the ability to be present.

There are some factors which are warning signals for complicated grief, suggesting that the bereaved person will find it particularly difficult to adapt to the situation after the death of the person they love. Risk factors include sudden unexpected death, traumatic death, loss of a child and loss of a partner with whom the relationship had been ambivalent ('can't live with, can't live without').[39] Depression is common in the bereaved and associated with the period of increased mortality.[39]

For many children, a grandparent is the most secure adult in their life as social disintegration and mobility may leave the child very dependent on the grandparent. It has been estimated that on average across the UK, in every school class there are approximately two children bereaved of a person close to them such as a grandparent and one child bereaved of a parent or sibling.[40]

Thus the way in which we provide care of the dying patient and their family will influence the next generation's ability to cope with illness and death.

Conclusion

Provision of high-quality care for those nearing the end of life is one of the hallmarks of a civilized society. The way in which we care for the most vulnerable, the way in which we value the individual and work to help them achieve their last goals in life, reflect on us as professionals. The absolute finality of death should never be taken lightly and the importance of care for those left behind is also crucial. The way in which we live and the way in which we die affect all around us and live on in the memory of others for a lifetime.

Key points

- Palliative care improves experiences of persons with terminal illnesses.
- Patients and families should be involved in end-of-life decisions.
- Assisted dying remains a controversial issue.
- There is increased awareness that end-of-life care is appropriate for patients other than those with cancer, for example, patients with heart failure and dementia.

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PART 3

Global Healthcare Systems

CHAPTER 137

Improving quality of care

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Introduction

Throughout most of history, medical care was delivered to an individual patient by an individual clinician. Public health services were rarely available and infection control practices were poorly understood. Institutional care was uncommon and reserved for those with means to afford the medical services. Over the last century, medical care has drastically changed through the development of antibiotics, immunizations, and new surgical techniques. The world's population is now growing rapidly, is ageing, and is requiring more health services. Population-based medicine has become a priority as cost, volume and efficiency became critical issues in meeting the growing healthcare demands of the medical consumer.

From provision of services to meeting standards of practice, the healthcare industry is under increasing pressure to provide the highest level of services to the greatest number of recipients. In an era of limited healthcare dollars, practitioners often must do more with less, yet medical advances and fear of litigation drive the cost of care upward. For these reasons, efficient, high-quality care is of increasing importance. Consumer groups, medical societies and healthcare organizations have been at the forefront in promoting quality in healthcare. With a collective voice, these groups have promoted change in the healthcare system. Although slower than many other industries, the healthcare establishment has recognized the importance of delivering quality goods and services.

With the advent of computers, the growth of the pharmaceutical industry, and advances in diagnostic technologies, the level of medical sophistication has risen dramatically. Clinicians and patients are now afforded a multitude of therapeutic options unavailable only a few years before. As with other industries, however, quantity of services does not automatically equate to quality of services. It is necessary to critically evaluate not only medical treatments and techniques but also the process by which medicine is delivered to the healthcare consumer. Defining quality, measuring performance and changing ineffective practices must now become routine activities as medicine moves toward more efficient and effective methods of healthcare delivery.

The history of quality

The history of quality in business

In 1906, the International Electrotechnical Commission (IEC) was established to provide uniformity to the electrotechnical field. (See Appendix 137.1 for organizational abbreviations.) The IEC promoted quality, safety, performance, reproducibility and environmental compatibility of materials and products. This was the first organization to develop international standards of business practice.

The International Federation of the National Standardizing Association (ISA) was another organization, focused on mechanical engineering, which set standards for industry and trade from 1926–1942. After ISA dissolved, a delegation of 25 countries convened to create a new organization to unify the standards of industry and production practices. In 1947 this organization, the International Organization for Standardization (ISO), was established in the United Kingdom to oversee the manufacturing and engineering trades.

The ISO is a federation of non-governmental agencies with membership from 163 countries across the world.[1] The ISO has developed international standards by which trade, technology and scientific activities can be measured. Companies may choose to be certified by the ISO-9000 quality management system. This certification ensures a minimum standard by which business processes, quality management and safety are maintained.[1] ISO certification is especially important for international and intercontinental business to ensure a uniform delivery of goods and services. The healthcare industry is one of many fields that may be evaluated in the ISO method. At this time ISO has developed 187 work item standards under the technical sector of health, safety and environmental.[2] Although used in some

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countries to evaluate medical practices, it is not the widely accepted model for evaluation of the healthcare system.

Around the same time that ISO was created, Dr W. Edwards Deming, a physicist and statistician from the United States, developed a new process for quality improvement in business. Through this process, all members of a work unit were responsible for continuous monitoring and improvement of products along all steps of production. High frequency errors were identified, corrected, and the resulting outcome monitored for improved quality. Any step in the production process could and would be a continuous target for revision. In this method, focus was shifted from the specific error of an individual to the systemic faults that allowed an error to go unnoticed or proceed uncorrected. The workforce was thus empowered to identify problems and institute a plan of correction. Deming introduced this process which is now known as Continuous Quality Improvement (CQI) and also referred to as Total Quality Management (TQM), Quality Assurance (QA) or Performance Improvement (PI). Used in Japan, TQM quickly led to a revolution in the efficient manufacturing of high-quality goods.

Deming knew that successful management of a complex process or problem required the focused attention of a team of individuals. Although each member was uniquely skilled in a task, the team worked together in developing solutions. The TQM process is well suited for quality improvement in the complex healthcare environment, but has not historically been embraced by the medical establishment. The narrow view that blame for errors be placed on a sole individual and that physicians be allowed autonomous control over medical processes has hindered the acceptance of TQM. This view is changing as organizations realize that medical errors and inefficiencies are usually the result of systemic problems that require multifactorial solutions.

The evolution of quality in healthcare

One of the first efforts to standardize medical delivery occurred in 1917 with the 'Minimum Standard for Hospitals' programme set forth by Drs Franklin Martin and John Bowman of the American College of Surgeons (ACS). A one-page, five-point set of criteria was crafted to assess the quality of hospitals[3] (see Table 137.1). In 1918, only 89 of 692 hospitals surveyed met the minimum criteria.

The ACS was responsible for hospital accreditation until 1952 when the Joint Commission on Accreditation of Hospitals (JCAH) was established to take on this responsibility. Led initially by Dr Arthur W. Allen, the JCAH published standards for hospital accreditation in 1953. The JCAH initiatives were also incorporated outside of the United States with Canada offering its own accreditation through the Canadian Commission on Hospital Accreditation in that same year. Over the next two decades, the JCAH grew to include the review of long-term care facilities in 1966 and subsequently mental health, dental, ambulatory care and laboratory facilities. In 1987 JCAH was renamed the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to encompass the variety of services and activities offered.[4] The organization was rebranded in 2007 and is now generally referred to as 'The Joint Commission'.

Table 137.1 The Minimum Standard.

'The Minimum Standard' American College of Surgeons 1917
1 That physicians and surgeons privileged to practice in the hospital be organized as a definite group or staff.
2 That membership upon the staff be restricted to physicians and surgeons who are
a full graduates of medicine in good standing and legally licensed to practice
b competent in their respective fields
c worthy in character and in matters of professional ethics
3 That the staff initiate and, with the approval of the governing board of the hospital, adopt rules, regulations, and policies governing the professional work of the hospital.
4 That accurate and complete records be written for all patients and filed in an accessible manner in the hospital.
5 That diagnostic and therapeutic facilities under competent supervision be available for the study, diagnosis, and treatment of patients.

The Joint Commission has been a world leader in healthcare accreditation and a prototype for further development of organizations that monitor and measure the quality of healthcare delivery. Over the past two decades the interest and efforts in healthcare quality have grown exponentially. A variety of national and international organizations have evolved to assist the healthcare industry in meeting new consumer and regulatory demands for high-quality services and programmes.

Organizations leading healthcare quality improvement

In the United States, the Agency for Healthcare Research and Quality (AHRQ), previously the Agency for Healthcare Policy and Research (AHCRP), is a leader in healthcare quality initiatives. Founded in 1989, this agency of the US Department of Health and Human Services has a mission to improve the healthcare quality, safety, efficiency and effectiveness for all Americans. AHRQ awards millions of dollars in grants to further evidence-based, outcomes research related to healthcare quality improvement. Federal legislation authorizes AHRQ to coordinate health partnerships, support research, and advance information and technology systems. Of the many projects that are overseen by AHRQ, the United States Preventive Services

Task Force (USPSTP) and Consumer Assessment of Health Plans (CAHPS) are most prominent. The AHRQ also publishes data on quality and trends in healthcare effectiveness and patient safety. For the past seven years, AHRQ has produced the National Healthcare Quality Report and the National Healthcare Disparities Report.[5]

The USPSTF is a 15-member, private-sector panel of experts, first convened by the United States Public Health Service in 1984 to develop and assess evidence-based preventive service measures. The hallmark publication of this taskforce titled *Guide to Clinical Preventive Services* was published in 1989, with a second edition released in 1996 and third edition in 2002.[6] Although clinicians and healthcare societies do not always agree upon the details, these guidelines are frequently cited as 'best evidence' and considered to represent the 'standard of care' in preventive medicine services. This agency has developed recommendations for adults and children in the clinical areas of: Cancer, Heart and Vascular Diseases, Injury and Violence, Infectious Diseases, Mental Health Conditions and Substance Abuse, Metabolic, Nutritional and Endocrine Conditions, Musculoskeletal Disorders, Obstetric and Gynaecological Conditions, Vision and Hearing Disorders, and Miscellaneous conditions.

CAHPS is an organizational databank of healthcare information used by consumers, employers and health plans in evaluating heath care systems and services. Surveys and reporting instruments are used to collect and present information on healthcare providers such as Medicare and the Federal Employees Health Benefits Program. In the private sector, the National Committee for Quality Assurance (NCQA) reviews the quality of managed care health plans. Established in 1990, this non-profit group also accredits the healthcare organizations.

NCQA uses the Healthcare Effectiveness Data and Information Set (HEDIS) tool to measure and report the performance of health plans and physician practices. More than 90% of US health plans use the HEDIS system which consists of 71 measures and 8 care domains. Such measures could include lead screening in children, blood pressure control and smoking cessation counselling.[7]

The Institute of Medicine (IOM) is another leader in the development of quality healthcare in America. This non-profit organization was chartered in 1970 as a segment of the National Academy of Sciences. The mission of the IOM is to work outside the governmental framework in providing an independent, scientifically based analysis of the healthcare system. 'Quality of Care' was defined by the IOM in 1990 as, 'the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge'.[8]

IOM formally launched the first of three phases of a quality initiative plan, beginning in 1996 with an intensive review of the state of healthcare in America. In a statement declaring 'The urgent need to Improve Health Care Quality', the IOM began focusing on overuse, underuse and misuse in medical care. During Phase Two, the Quality of Health Care in America Committee convened and has since published several reports, including *To Err is Human: Building a Safer Health System*, and *Crossing the Quality Chasm: A New Health System for the 21st Century*. The most recent IOM quality improvement publications have focused on patient safety and performance measures. These titles include: *Rewarding Provider Performance: Aligning Incentives in Medicare; Preventing Medication Errors: Quality Chasm Series;* and *Performance Measurement: Accelerating Improvement*.[9]

The IOM has lobbied for an error reporting system and legislation to protect those who report errors in an effort to promote quality improvement strategies. Twenty 'Priority Areas for National Action' have been established based on diseases or conditions that may be best managed using clinical practice guidelines (see Table 137.2). The IOM has established six 'Aims for Improvement' in health system function. Healthcare should be: (1) safe, (2) effective, (3) patient-centred, (4) timely, (5) efficient, and (6) equitable. The Committee has also identified '10 simple rules for [healthcare system] redesign' which change the focus of healthcare from provider driven to consumer/system driven care (see Table 137.3).

Table 137.2 Health priority areas.

20 priority areas for improvement in healthcare quality
• Care coordination
• Self-management/health literacy
• Asthma
• Cancer – focus on colorectal and cervical cancer
• Children with special healthcare needs
• Diabetes – focus early disease management
• End of life with advanced organ system failure
• Frailty associated with old age
• Hypertension – focus on early disease management
• Immunization – children and adults
• Ischaemic heart disease
• Major depression – screening and treatment
• Medication management – preventing medication errors and antibiotic overuse
• Nosocomial infections – prevention and surveillance
• Pain control in advanced cancer
• Pregnancy and childbirth – appropriate prenatal and intrapartum care
• Severe and persistent mental illness – focus on treatment in the public sector
• Stroke – early intervention and rehabilitation
• Tobacco dependence treatment in adults
• Obesity

Table 137.3 Rules for health system redesign.

Ten rules for health system redesign
1 Care is based on continuous healing relationships.
2 Care is customized according to patient needs and values.
3 The patient is the source of control.
4 Knowledge is shared and information flows freely.
5 Decision making is evidence based.
6 Safety is a system property.
7 Transparency is necessary.
8 Needs are anticipated.
9 Waste is continuously decreased.
10 Cooperation among clinicians is a priority.

In the United Kingdom, healthcare is provided nationally through a national healthcare service programme within each country. In England, the National Health Service (NHS) has received annual reviews since the Commission for Health Improvement (CHI) was established in 1999 by the national government. In April 2004 this organization was replaced by the Healthcare Commission (HC), which was charged with the task of reviewing and improving the quality of healthcare in the NHS and in the private sector. In April, 2009 the Healthcare Commission merged with the Mental Health Act Commission and the Commission for Social Health Inspection to become the Care Quality Commission (CQC). The CQC collects data on quality of healthcare services that are delivered on a local and national level. This data is available for public inspection. On 1 October 2010, legislation established five essential standards of quality and safety that are required for all agencies that provide health services.[10] These standards are as follows:

1 the recipient is informed and involved at all times
2 care and treatment will meet individual needs
3 the recipient will be protected from harm and provided safe care
4 care is provided by qualified individuals
5 care providers will be involved in quality improvement.

This legislation moves the NHS quality assurance process from an inspection-reporting process to a continuous quality improvement process.

Other countries in the United Kingdom have their own regulatory agencies and standards for healthcare services. In Scotland, the Regulation of Care (Scotland) Act 2001 established the Scottish Commission for the Regulation of Care (SCRC) based on a set of National Care Standards. The standards define the expected quality of service that is provided and allows for regulatory reports to be generated for health service agencies. In 2004, the Healthcare Inspectorate Wales (HIW) was established to review the quality and safety of all healthcare provided in this country. In Northern Ireland, the Regulation and Quality Improvement Authority (RQIA) monitors and inspects the Health & Social Care Services in Northern Ireland. This agency was established in 2003.

In Australia, evaluation and accreditation of medical practice takes place through the Australian Council on Healthcare Standards (ACHS) and its subsidiary the Australian Council on Healthcare Standards International (ACHSI). The ACHSI uses Australian standards and modifies these to be culturally and internationally appropriate. ACHSI then works in partnership with healthcare accreditation bodies in Ireland, India, New Zealand, Bahrain and Hong Kong through exchange surveyor programmes.

Established in 1974, ACHS is an independent body comprised of healthcare leaders, governmental representatives and consumers. ACHS accredits programmes using a standardized model called the Evaluation and Quality Improvement Program (EQuIP). EQuIP sets standards in two broad categories: (1) patient care services across the continuum of care, and (2) the healthcare infrastructure. EQuIP standards are revised every four years. On 1 July 2011 the version EQuIP5 will be implemented.

ACHS also provides comparative information on the processes and outcomes of healthcare through the Clinical Indicator Programme. Using 23 Clinical Indicator Sets with over 350 Clinical Indicators, data submitted from a healthcare organization can be quantitatively measured and objectively compared with other organizations and with national aggregate data. Outlying data generates a 'flag', which can alert the organization to quality control problems.[11]

In 2006 the Australian Commission on Safety and Quality in Health Care (ACSQHC) was established to develop a national framework for improving safety and quality across Australia.[12] This commission is charged with:

- identifying priority healthcare issues and setting policy directions
- disseminating knowledge and advocating for heath safety and quality
- public reporting of health safety and quality data
- coordinating and developing national health and safety data bases
- advising Health Ministers
- recommending national safety and quality standards.

Australia is also the original host country of The International Society for Quality in Health Care (ISQua), which moved to Ireland in 2008. This non-profit organization 'Accredits the Accreditors' and provides services and information on healthcare quality to medical providers and consumers. Over 50 healthcare organizations, standards and surveyor programmes are accredited through ISQua.[13] ISQua hosts an annual international summit to discuss performance indicators and promote a multidisciplinary approach to quality improvement

programmes. Participants include health policy leaders, researchers, healthcare professionals and consumer organizations. The ISQua also supports the *International Journal for Quality in Health Care*, a peer-reviewed journal in its 22nd year of publication.

Models for evaluating quality

The approach to quality in healthcare bears many similarities to quality improvement in the commercial sector by focusing on key issues of safety, effectiveness, consumer satisfaction, timely results and efficiency. Within Europe, there is much diversity in the oversight and governmental mandates for quality of healthcare practice. Most legislation surrounds the health system and hospital accreditation process, with less emphasis placed on individual clinical practices. Based on the established healthcare and payer system, each country may address quality control quite differently.

To better understand the most common methods of measuring healthcare quality, a survey of European External Peer Review Techniques (ExPeRT) was initiated.[14] The results of this ExPeRT Project, revealed four commonly used quality improvement models: healthcare system accreditation, ISO certification (both discussed previously in this chapter), the European Foundation for Quality Management (EFQM) Excellence Model, and the Visitatie peer review method.

The EFQM is a global non-for-profit foundation founded in 1988 by presidents of leading European companies and which uses the 'EFQM Excellence Model' for assessing the quality of an organization. The framework for this TQM approach includes nine criteria by which an organization is evaluated on 'what it does' and 'what it achieves'. A Quality Award is presented after a process of self-assessment and internal review. Members within the EFQM foundation learn from each other and share best practices for improving the quality of service provided to the consumer.[15]

The Visitatie model originated in the Netherlands and focuses on medical practice specifically, rather than on business practices broadly. Visitatie is a peer review consultation process that uses practice and practitioner-derived guidelines to evaluate patient care. Emphasis is placed on individual and team performance, not organizational structure or outcomes. Unlike other methods, Visitatie does not result in a certification or accreditation award. Because the focus is on improving care through peer feedback, there is no 'pass/fail' or punitive outcome. This model is becoming popular across Europe as a method for personal and peer review of medical care. Groups who have used this consultation approach to practice management reported more success and fewer barriers when implementing quality improvement changes in practice.[16]

Quality improvement in geriatrics

The elderly population is prone to adverse outcomes, especially when healthcare delivery is fragmented. Research has demonstrated that adverse health events are more likely to occur in the elderly population and that the risk of adverse hospital events is twice as high for individuals over age 65.[17,18] Preventive medicine for seniors includes identifying patient safety issues that can lead to functional decline and poor health outcomes. Identifying risk factors for decline and providing early intervention is effectively approached though a healthcare team-based TQM process.

Quality in healthcare has evolved from a reactive Quality Assurance (QA) model (see Figure 137.1), to a proactive TQM model (see Figure 137.2). Instead of focusing on compliance and adherence to external regulations or standards (QA model), TQM focuses on the continuous process of improving care relative to current internal practices. TQM involves not only change in practices on an individual level, but also change in process on a larger scale that can benefit a broader population.

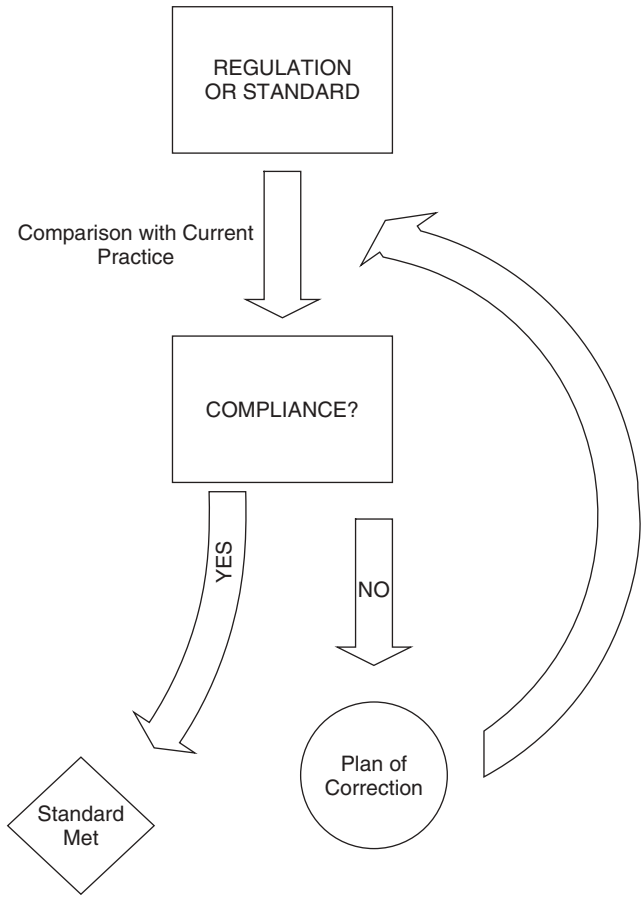

Figure 137.1 Quality Assurance Model.

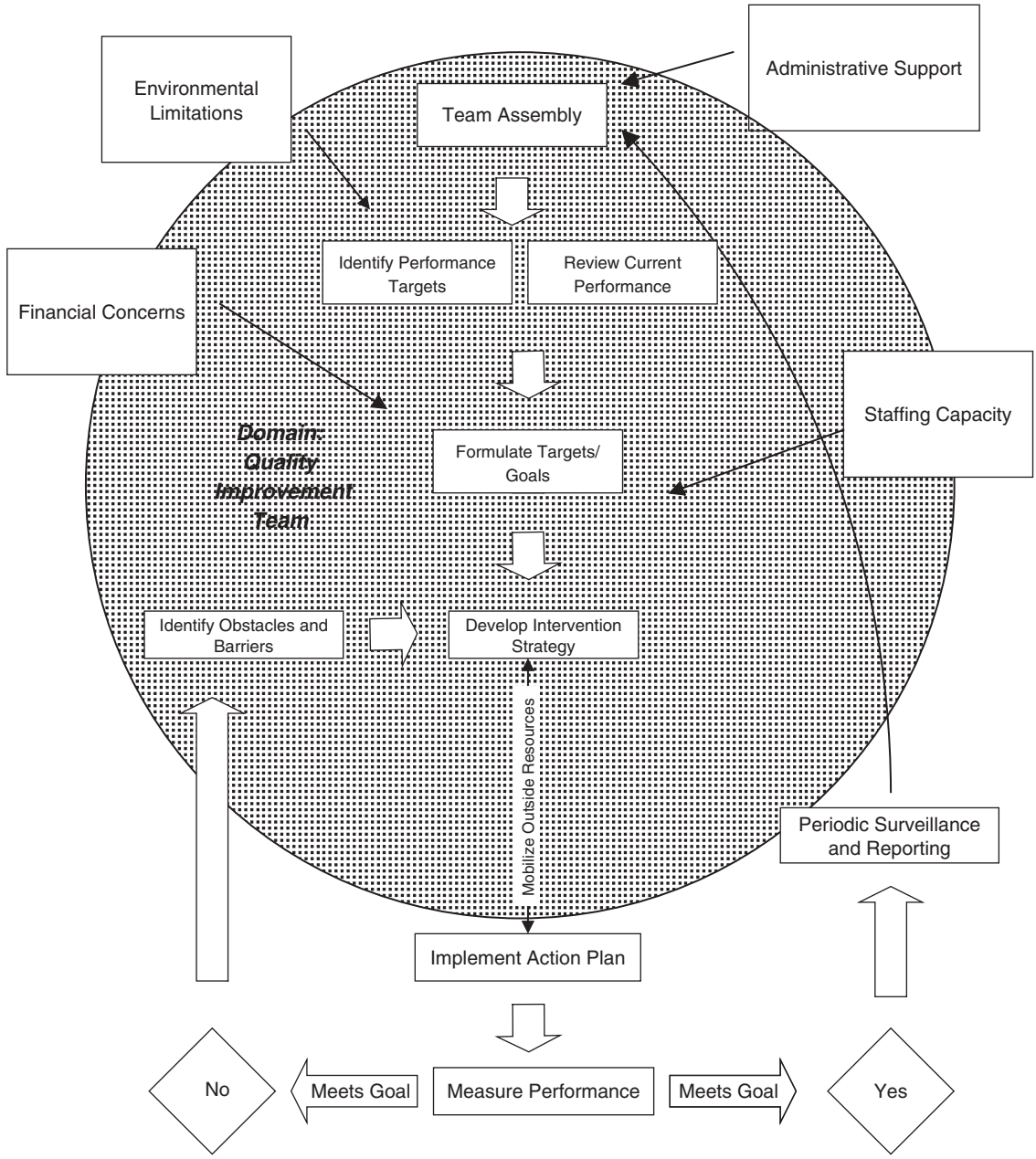

Figure 137.2 Total Quality Management (Continuous Quality Improvement) Model.

In the TQM team process, each discipline reports data collected on patient care since the previous team meeting, as well as areas of ongoing concern or newly identified issues. The team discusses markers (indicators) of quality and establishes targets to achieve by the next meeting. The team then develops a plan for achieving these targets. A method of measuring performance and collecting data is established. An individual or subcommittee is then assigned to carry out the quality improvement protocol and provide a progress report at the next meeting. If the goals are achieved, data continues to be tracked over time to identify trends in performance and to maintain the established goals. If previously established quality targets are not met, barriers or obstacles are explored.

Geriatricians are in a unique position to take a lead in the healthcare quality improvement process. Interdisciplinary management and teamwork are at the core of geriatrics training and practice. Geriatricians are comfortable entrusting responsibility to team members and sharing in the problem-solving process. This is a requirement for

the success of TQM programmes. Geriatricians are also more likely than other physicians to have experienced the TQM process, as this is a routine activity in long-term care facilities. Through TQM, data on events such as falls and dehydration are tracked and shared with the staff at regular intervals. Trends are then discussed and solutions proposed when outlying results are identified.

Quality indicators

In the United States, markers for quality in nursing home care, termed 'Quality Indicators' have been developed and tracked by the federal government through the completion of the required Minimum Data Set (MDS) resident evaluation questionnaire[19,20] (see Table 137.4). Quality is assessed on these indicator domains using 'Quality Measures'. These measures include sentinel events such as faecal impaction or dehydration, and incidence/percentage of residents with certain conditions such as indwelling catheters and pressure ulcerations. Data on these measures is collected and reported federally through the MDS, and facilities are then compared against local and national facility averages. Facilities with outlying rates on the quality measures are 'flagged' which may prompt investigation or oversight by the state nursing home regulatory board.

Concerns have been raised about the accuracy and utility of data extracted from the MDS. For this reason, the previous version of MDS 2.0 has recently been replaced by version 3.0, which directly includes nursing home residents in the assessment process and employs more standardized

Table 137.4 Measures of nursing home quality.

Domain/Quality Indicator	Quality Measure
Accidents	• Incidence of new fractures • Prevalence of falls
Behaviour/Emotional Patterns	• Prevalence of behavioural symptoms affecting others (high and low risk individuals) • Prevalence of depression with no antidepressant therapy • Percent more depressed or anxious
Clinical Management	• Use of 9 or more different medications
Cognitive Patterns	• Incidence of cognitive impairment
Elimination/Incontinence	• Prevalence of bladder or bowel incontinence • Prevalence of occasional or frequent bladder or bowel incontinence without a toileting plan • Percent with a catheter inserted • Prevalence of faecal impaction
Infection Control	• Percent given influenza vaccination • Percent given pneumococcal vaccination • Percent with a urinary tract infection
Nutrition/Eating	• Percent with excess weight loss • Prevalence of tube feeding • Prevalence of dehydration
Pain Management	• Percent with moderate to severe pain
Physical Functioning	• Percent spending most of their time in bed or chair • Percent with declining ability to move about their room • Percent with increased activities of daily living needs • Incidence of decline in range of motion
Psychotropic Drug Use	• Prevalence of antipsychotic use in the absence of psychotic conditions (low- and high-risk individuals) • Prevalence of any antianxiety/hypnotic use • Prevalence of hypnotic use more than two times in the last week
Quality of Life	• Percent physically restrained • Prevalence of little or no physical activity
Skin Care	• Percent at high risk with pressure sores • Percent at low risk with pressure sores
Post-Acute Care	• Residents with delirium • Residents with moderate to severe pain • Residents with pressure ulcers

protocols for obtaining resident data. Schnelle and others have published a tremendous body of literature on the care process and health outcomes in nursing homes based on information obtained from the MDS.[21–23] In some cases the quality measures are strongly associated with a positive or negative clinical outcome.[22,23] In other cases, the indicators do not predict an event that might be expected based on the provided data.[21,22] A recent systematic review failed to find strong and consistent evidence that MDS data was a reliable or valid measure of the nursing home quality indicators.[25]

The existing quality indicators do not adequately address quality of life (QOL) and provision of daily care services. To address these issues, an expert panel of geriatricians convened and developed an additional set of quality indicators that complements the existing MDS-derived indicators. These measures may better track the quality of day-to-day care in nursing facilities.[24] The quality indicator domains include (1) preferences for daily life activities, (2) frequency and form of activities of daily living (ADL) assistance, (3) activity, (4) assistive devices, (5) goals of care, and (6) communication. Although considered markers of quality care, many of these QIs are successfully achieved only in 'the best nursing homes'. Thus, although a target to strive for, these QIs may not be attainable for the average facility.

Geriatric medicine organizations focus on quality

Interest groups and specialty organizations such as the American Geriatrics Society (AGS), American Medical Directors Association (AMDA), British Geriatric Society (BGS), and the Australian and New Zealand Society for Geriatric Medicine (ANZSGM) have taken a leadership role in bringing global quality improvement initiatives to the ageing population. These organizations work within the healthcare framework and governmental regulations unique to each country. Whereas national physician organizations focus efforts widely across the healthcare system, these specialty groups address ageing specific healthcare issues.

The ANZSGM has established a series of position papers that outline standards for geriatric care in Australia. The most recent paper is on transitions of care, a process that is especially challenging for older adults.[26] Care transitions are of increasing importance in designing safe and effective health systems for the elderly. The Australian Institute of Health and Welfare has published a systematic review assessing the evidence for transitions in care of people with dementia. This publication addresses care transitions and pathways through the Australian healthcare system.[27]

The British Geriatrics Society has also published numerous position papers, clinical guidelines and best practice guides on the care of elders in the United Kingdom. These papers increasingly focus on safety and quality of care.[28] One way the United Kingdom has addressed the quality of hospital care for seniors with orthopaedic trauma is through the development and expansion of orthopaedic rehabilitation units. These wards provide multidisciplinary care and partnership between geriatric medicine consultants and orthopaedic surgery physicians. Although individual studies have demonstrated some benefits in reducing length of stay and improved functional outcomes, a Cochrane Database analysis on the subject did not find conclusive evidence that coordinated multidisciplinary hip fracture care improved long-term post-surgical outcomes.[29–31] Small benefits have been noted in activities of daily living and mobility in the immediate postoperative period.[32]

In the United States, medical organizations regularly lobby congress on behalf of the geriatric medicine profession and elderly patients. The institution of a prescription drug benefit for Medicare health insurance beneficiaries is one example of the influence of healthcare organizations and consumers on healthcare policy and quality. The American Medical Directors Association (AMDA) has been a tremendous advocate for quality, focusing primarily on the long-term care setting. AMDA has created clinical practice guidelines for nursing home care and has established a certification process for medical directors in these facilities. Within the medical community, AMDA has pressed for a change in approach to long-term care and is viewed as the leading organization in long-term care reform.

From a consumer perspective, the Leapfrog Group is an organization with great potential for influencing the quality of healthcare plans and services. Founded by Fortune 500 executives, this group of over 150 companies aims to improve patient safety by lobbying for computerized physician ordering systems, appropriate patient referrals to subspecialty hospitals, and uniform critical care staffing in intensive care units. The Leapfrog Group represents 37 million healthcare consumers and uses its healthcare benefit purchasing power to influence the insurance industry in delivering healthcare that meets these quality standards.[33]

Quality in the nursing home

When trying to improve quality of care, one must first characterize quality. Quality is the degree to which an outcome measures up to the expected gold standard. In healthcare delivery, a quality process or intervention is measured against a standard practice that is administered to an individual patient, in a given situation, with a particular problem. Deviations from the standard of care affect the quality of care. Patients and their families expect health services to meet or exceed the standard of care but may not understand what constitutes a reasonable standard.

To maintain the highest quality of care, continuous system-wide observation, evaluation and monitoring are needed. Healthcare managers are responsible for

establishing performance standards for their staff and ensuring that these standards are met. The employees should feel comfortable providing feedback to the supervisors when aspects of healthcare delivery require improvement. Managers must work with facility administrators to negotiate the resources necessary to allow the staffing team to carry out daily duties in an effective manner. Many quality improvement teams use the term 'continuous quality improvement' to describe this process because maintaining quality is an ongoing activity.

Identifying the problem

Areas of concern are brought to the attention of the healthcare manager through a variety of avenues. In the long-term care setting, a nursing home administrator collects and catalogues this information through direct or indirect contact with residents, their families and the facility staff. Administrators should also expect feedback and performance reports from the medical director and attending physicians working within the facility. Good communication between all members of the facility is essential to ensure a positive resolution to a perceived problem.

Identifying a problem shortly after it occurs and promptly initiating a plan of correction is paramount. Timeliness often affects outcome. First impressions are very important when a patient first enters a long-term care facility. Every effort must be made to ensure that the transitional period is a positive experience. After acclimating to the facility, it is important for the residents to have periodic meetings to discuss the plan of care. These meetings help to maintain a good line of communication and empower the resident to be a participant in the healthcare process.

The nursing home administrator

The nursing home administrator is responsible for the overall care within a facility and must handle all areas of concern that arise. Problems should be examined and categorized to better understand the origin of the difficulty. This information can alert the administrator to potential problems or areas of concern that need to be addressed. Nursing home administrators should to be visible and accessible to families and residents, as well as staff, when responding to facility concerns. When complaints increase, the facility administrator must investigate and take steps to correct the problem.

Nursing care

There are many inter-related components that impact the care provided by facility nursing staff. One of the most important areas, besides ensuring skill proficiency in the nursing staff, is the organization and function of nursing 'systems'. Systems of nursing practice must be in place in order to deliver high-quality care. Two examples of these 'systems' include the structure of the nursing staff and the function of the nursing staff. Critical components of these systems include staffing patterns, delegation of work assignments, supervision and evaluation of performance. Educational programmes for the nursing staff should also be provided on an ongoing basis. The nursing assistants as well as the licensed nurses need to learn and review basic skills as well as specialty techniques necessary for the care for their residents. Ensuring a smoothly running system requires responsibility, good communication, respect and clearly defined expectations. Nurses and administrators must view their interactions as two-way streets in order to build and maintain well-functioning nursing systems within a facility.

To maintain high-quality care, nurses must be able to identify residents 'at risk' for unwanted outcomes. This can be performed during weekly multidisciplinary 'high risk' needs assessment meetings for problems such as skin breakdown, falls and confusion. Because mental status may change quickly and without notice in older adults, medical status must be assessed frequently. Nursing managers should periodically review high-risk individuals to help assure optimal care. Routine nurse manager oversight can address these and other potential problems before serious issues occur.

Quality improvement meetings

Members of the quality improvement team should include pharmacy, lab, attending physicians, the medical director, nursing, therapy, dietary, maintenance, activities, social service, medical records and administration. Many long-term care facilities meet only on a quarterly basis to discuss various issues of quality care. This is not frequent enough. Monthly meetings help improve the communication of information and remind everyone of quality initiatives and areas for improvement.

Pharmacy should present the monthly number or percentage of residents on antipsychotics, anxiolytics and antidepressants. By reassessing the continued need for psychotropic medication in nursing home residents, dosing and prescribing reduction frequently occurs. Pharmacy should also report the incident and type of medication errors and assist in developing methods to reduce errors. To minimize possible drug–drug interactions, a goal of nine medications or less per resident should be a target at the facility.

The laboratory service provider should report the number of microbial cultures performed during that month with those that were negative as well as positive. Organisms that are identified are reviewed along with antibiotic sensitivity patterns. Timeliness of the cultures reported to the facility and institution of appropriate antibiotics are

reviewed. Trends in organisms, antimicrobial sensitivity and clustering of infections should be assessed. Laboratory services should also investigate unnecessarily prolonged return of blood work reports and the effectiveness of data transmission to the nursing facility.

Each month, nursing should present the number of residents who developed decubitus ulcers, have indwelling foley catheters, and received physical restraints. To reduce the rate of injuries and falls, each facility should strive to be restraint-free.[34] The rate of facility acquired decubitus and indwelling foley catheters, should be under 5%. If rates rise above 5%, action should be taken to justify or remedy this trend. Weight loss and excessive gain should be reported every month, including a probable cause and a plan of correction. Awareness is key and all disciplines can participate in weight loss prevention protocols.

Incident reports should be reviewed monthly. Investigation of resident incidents should include type, location where the incident took place, time of day (during which shift), weekend versus weekday, and degree of injury or impact. Trends or patterns in this data should be noted and a plan for incident reduction implemented. Employee incidents should also be evaluated. An increase in employee incidents and injuries is often directly related to employee dissatisfaction.

Patient census should be reviewed at each meeting along with admissions, transfers to and from the hospital, discharges to home/another facility and deaths. When looking at nursing home admissions, one should also look at the source of their admission. Was the new admit from a hospital, and if so, which hospital? Are admissions trending up or down? What days and times are the hospital admissions arriving at the nursing home? Transfers to the hospital or emergency department should also be tracked. Was the transfer preventable? Are certain shifts or floors more likely to transfer residents out for urgent evaluation? This valuable information allows the nursing home administrator and director of nursing to identify staffing or skill deficiencies within the facility.

When providing therapy to the long-term care resident, the therapist needs to keep a record of the functional level prior to therapy, the number of days in therapy, the functional level when therapy was discontinued, and disposition upon discharge. It has been demonstrated that extending therapy a few more days often improves overall outcome. Therapy services can use this information as a marketing tool. The department may display, in a graphic format, the functional level or residents prior to illness, upon initiation of therapy and upon discharge of therapy.

The quality improvement process that is discussed and monitored during team meetings should be documented in an organized and systematic manner using a standardized reporting process (see Table 137.5). Topics relevant to patient care quality (e.g. falls) are selected by the team. Indicators of quality (e.g. fall rate, injurious falls, number of fractures) are identified and a target rate for the facility is established (e.g. <5% of falls resulting in injury). Data on patient outcomes is collected within the facility and compared with the established indicator target. If current standards fail to meet the target, areas for improvement (e.g. reducing nighttime falls) are identified and a plan of action established (e.g. scheduled toileting at bedtime). During the follow-up phase, data on the indicators is again collected to determine if the intervention has resulted in successful achievement of the established goals.

Quality in acute care practices

Hospital accreditation

The internationally recognized Joint Commission on Accreditation of Healthcare Organizations (JCAHO) mission is to provide accreditation and performance review for the safety and quality of healthcare facilities. Established over 50 years ago, this independent non-profit organization reviews not only hospitals, but also a variety of healthcare facilities such as nursing homes, home care organizations, healthcare networks, outpatient centres and clinical laboratories. Accreditation is a marker of quality valued by the community and used to promote the excellence of an institution.

Accreditation takes place after undergoing an on-site survey by a team of medical and business professional. All aspects of care are reviewed, including compliance with safety procedures, patient care processes and the work environment. Hospital accreditation is valid for three years. JCAHO uses standardized performance criteria that were developed with the expertise and guidance of healthcare leaders in academic medicine, business and governmental agencies.

In other parts of the world, the hospital evaluation process may take place through national or international regulatory organizations. In Europe, hospital accreditation first was introduced in Spain through the Catalan Hospital Accreditation Programme (CHAP) in the early 1980s.[35] Due to financial setbacks, this programme was not continuously active until 1991. In the United Kingdom, a sustained accreditation programme has been in place since 1990. Results of a 2004 survey indicated that 18 European countries were formally utilizing or implementing a hospital accreditation programme.[36] By 2009, 18 different accrediting organizations were active throughout Europe.[37]

In the United Kingdom, healthcare facility accreditation began in 1989 through two organizations: the Caspe Healthcare Knowledge Systems (CHKS) and the King's Fund Organisational Audit (KFOA). These non-governmental organizations were first developed to oversee the National Health Service hospitals but have grown to include accreditation of public and community healthcare centres. The

Table 137.5 Continuous Quality Improvement Report.

Topic _____ Dept. _____
Report Date_____ _____ Initial Report_____ Follow-up

I. Process Planning
Reason for selecting topic_____
Starting Date_____
Frequency of Monitoring_____
Sampling Population_____
Source of Information_____ Records _____ Survey
_____Observation _____ Other
Method for Data Collection_____

II. Indicators and Data Presentation

Indicator	Goal (Frequency or %)	Data (Numerical)	Data (Percent)

Interpretation of Data and Comparison to Established Goals:

III. Analysis and Plan of Improvement

A. Areas for Improvement		Obstacles or Barriers	
B. Action Plan	**Key Personnel**	**Initiation Date**	**Completion Date**

IV. Follow-up and Re-evaluation

Indicator	Date to Re-evaluate	Key Personnel	Date for Follow-up Report

Report Prepared and Reviewed by:

Name Title Date

KFOA became the Health Quality Service (HQS) in 1998 and was acquired by CKHS in 2005. Accreditation reports are available for public inspection in the United Kingdom and a handful of other countries, but in general are not available to healthcare consumers in Europe. Although the majority of accredited programmes are hospital-based, evaluations of community and outpatient care centres are evolving in several European countries.

Both JCAHO and CKHS offer international accreditation services. In 1999 JCAHO initiated an international programme for accreditation. To address the international differences in healthcare delivery, a 16-member task force developed 'international consensus standards' for the Joint Commissions International. This task force represents the healthcare concerns, values and governments of countries on six continents. CKHS offers consultation services within and outside of Europe and is accredited by ISQua to provide the ISO 9001 quality management systems for healthcare organizations.

The hospital environment

It has long been known by geriatricians that the hospital is a dangerous place for frail elderly individuals who are at high risk for iatrogenic complications. If immobility, delirium and nutrition are not addressed upon hospitalization, unwanted morbidity and functional decline can rapidly occur.[38,39] Altering the hospital environment to improve outcomes in the elderly has become a focus of research and a measure of quality in healthcare. *US News and World Report* magazine ranks United States hospitals and medical programmes each year. Among a host of factors used to evaluate quality, hospital-based geriatric services are included in this calculation.[40]

Over the past decade, several geriatric services have been developed with demonstrated benefit in reducing the risk of hospital-related morbidity and mortality. These programmes have largely targeted the prevention of delirium and reduction in functional decline. Hospitals are increasingly aware that reducing adverse events in the elderly is important not only for maintaining a positive public reputation, but in reducing healthcare costs.

Acute Care for the Elderly (ACE) units have been shown to decrease discharge to nursing homes and to improve functional outcomes at hospital discharge.[41,42] The general principles of ACE units include an interdisciplinary care approach, tailoring the hospital environment to reduce iatrogenesis, maximizing functional status, daily geriatric assessments with an active involved, specially trained nursing staff and proactive discharge planning. The implementation of ACE units in hospitals is growing.

The Geriatric Evaluation and Mangement Unit (GEMU) is another multidisciplinary care model linked closely to the inpatient hospitalization setting. GEMUs provide subacute care and rehabilitation in a setting that bridges hospital to home. The goals of GEMU care include maximizing functional, social and medical status through comprehensive geriatric assessment. Patients who would otherwise require nursing home placement receive dedicated medical and therapy services to regain lost independence. The GEMU model has demonstrated benefit in reducing rehospitalization, improving physical and cognitive functioning, reducing mortality and increasing the likelihood of living at home after discharge.[43] These outcomes are indicators of the quality and benefit of a multidisciplinary approach to care of the older adult.

Quality in the community setting

Home care

Medical care in the home has shifted from the historical single-provider model of the early 1900s to a team-based service with the advent of home healthcare organizations. This multidisciplinary approach has expanded the access and availability of healthcare services to homebound individuals. Australia has taken home care to an even higher level of sophistication with the 'Hospital in the Home' approach. This model provides hospital-like services to individuals at home who are acutely ill but unwilling to enter the hospital or for whom hospitalization is unlikely to provide any measurable health benefit. The quality of care for Hospital in the Home as measured by cost, patient satisfaction and medical outcomes, is at least equivalent to traditional hospital care.[44,45]

Patient care in the home is of increasing complexity and acuity. For organizations to meet the quality care standards expected by consumers, home-care services must be broad in scope and efficient in delivery. The success of Hospital in the Home and growth of home care is in part due to the advancement of portable medical technologies. Mobile radiology and laboratory services have expanded the diagnostic capabilities of home-care providers. The availability of intravenous access services and infusion devices have allowed more frail and debilitated elders to receive necessary intravenous therapies without transfer to the hospital or nursing home setting. Portable electrocardiogram monitors and serum analysis systems, although not in widespread use, now allow providers a more efficient and expedited evaluation of the home-care patient.

To address the question of how home health services improve the quality of medical care, the Agency for Healthcare Research and Quality, through the Centers for Medicare and Medicaid Services (CMS) in the United States, has developed a Home Health Quality Initiative project. CMS currently provides financial reimbursement for more than half of the home-care expenditures for seniors.[46] A set of 41 quality measures are used to evaluate home-care

agency services. These measures are based on outcomes data from the Outcome and Assessment Information Set (OASIS) national standardized home-care database. Quality measures are functionally based, such as improvement in toileting or improvement in bathing, but also include the utilization of emergency or hospital services.[47] Using the reported outcomes on these quality measures, certified home-care agency evaluations can now be reviewed online by the medical consumer.

Home monitoring and telemedicine systems are of increasing interest in the care of chronically ill seniors. A variety of products that record patient information, transmit data to a monitoring centre, or give patient reminders are now commercially available. Remote medical monitoring systems can intermittently or continuously monitor vital signs and disease symptoms using non-invasive and minimally intrusive sensors. These systems use internet, radio, or phone-line transmission of medical information to a hardware- or software-based system that acquires, stores and processes the data. Medical staff can examine the data in real-time or at periodic intervals. Alert parameters can be programmed to immediately notify the provider of abnormal findings. These systems are used almost exclusively in association with home healthcare services. Initial studies suggest that for chronic disease management, electronic home monitoring systems can reduce hospitalization rates and length of stay and improve disease control.[48–51]

The most basic home care technologies include personal alarm systems and emergency response telephones that make a voice connection between the patient and the response centre. This 'lifeline' monitoring system uses a self-activated call button that is often worn as a necklace or bracelet. More expansive and complex systems are being designed to monitor the home and activity of frail elders. The 'smart home' technology utilizes sensors placed throughout the home to track 'normal' daily activity and report potential emergencies by detecting deviations from typical activity patterns. These devices may improve the safety and security of older adults living at home, but conjure up unsettling images of an Orwellian world where 'Big Brother' is watching.

Database analysis in the United States

Large, centralized healthcare organizations, such as health maintenance organizations (HMO) and the Department of Veterans' Affairs Medical Centers (VAMC) in the United States, frequently use health database analysis to track costs, utilization of services and patient care outcomes. Data from these organizations is used for epidemiology studies and for population-based research on disease and healthcare services. Although cost containment may be a driving force in the monitoring of health statistics, these organizations have the infrastructure to use healthcare data for quality improvement purposes.

Because laboratory, radiology and pharmacy services are usually provided within the organization, utilization statistics may be readily available to the clinical and administrative providers. Often this information is tracked electronically within the organization. Practice patterns can be monitored and feedback sent to clinicians or departments to improve the delivery of patient care. Appointment backlogs, vaccination rates and cancer screening rates may be targeted by the organization. Goals for improving the delivery of healthcare can be set and trends measured after instituting a plan of improvement.

There is growing interest in a disease-based team approach to improve health outcomes. Common disorders that require regular monitoring or result in high use of urgent care services, such as diabetes and asthma, are often the target of these efforts. Using nationally developed practice guidelines or internally developed clinical care protocols, centralized healthcare organizations have the infrastructure to implement care processes to improve health outcomes.

Although clinical practice guidelines are not universally agreed upon in every detail, they are generally considered to represent a reasonable and achievable standard of care supported by current evidence-based research. Thus, adherence to practice guidelines may serve as a marker for quality care within an organization or clinical patient base. Pharmacy and clinical laboratory databases are used to provide individual feedback to clinicians on decision-making behaviour, compliance with national guidelines, and improvement in patient outcomes over time. The use of database monitoring to generate electronic reminders that prompt screening and disease management have demonstrated improvement in practitioner adherence to healthcare standards.[52–54]

Although database analysis offers much statistical information, ongoing problems include limitation of content, relative inaccessibility to information, lack of automated data and data mismatches.[55,56] This could be improved through new financial and technical support to HMOs interested in outcomes-based research.

Healthcare audit in the United Kingdom

In the United Kingdom, population-based review is conducted through a process called clinical audit. The National Health Service has used this method of quality improvement for over 20 years. Clinical audit is a 'systematic, critical analysis of the quality of medical care including the procedures used for diagnosis and treatment, the use of resources, and the resulting outcome and quality of life for

the patient'.[57] Clinical audit has evolved from a clinician-targeted to a system-targeted review that evaluates the outcomes of a quality improvement process.

Clinical audit is an internal method whereby a clinical practice, such as the frequency of ophthalmologic evaluation in diabetic patients or rate of influenza vaccination, is measured using medical record review. Performance markers are compared to accepted standards, practice guidelines, or previously established audit goals. If performance falls below expectations, a plan for practice revision is established and implemented. Follow-up audit is conducted to assess the success in achieving the targeted practice goals.

Clinical audit is a dynamic process that requires attention to changes in population demographics, health resources and advances in medical knowledge. Comparison of audit results between clinical sites or regions must account for this heterogeneity. The geriatric population itself is a heterogeneous group. For the elderly, important clinical outcomes are linked less to chronological age than to functional ability. A clinical audit outcome measure of cancer screening rates in a healthy 75-year-old population, for example, may be quite different than a chronically ill and debilitated 75-year-old cohort.

The success of a clinical audit requires a well-structured approach, appropriate time and appropriate resources. Too frequently, a problem is identified through the clinical audit but a plan of correction is not implemented or the outcome of the correction is never evaluated. This may be due to a lack of experience and time on the part of the auditors, who are often junior clinicians within the organization. Resources must be available if an organization plans to undergo a systematic review of a clinical issue with the intent to implement a meaningful change in clinical practice.

Large-scale clinical audits can require significant administrative support. Charts must be collected, data extracted and statistical evaluation performed. A protocol for change in practice must be developed with the input and agreement of clinical practitioners. Piloting the proposed change may be necessary to troubleshoot unforeseen barriers before implementing the plan on a larger scale. After an appropriate duration of practice, the clinical issue must be re-evaluated to determine if the new protocol has had an impact on the targeted outcome of the programme.

It is important that a clinical audit be viewed as a quality improvement activity and not as a means to emphasize personal shortcomings or to generate punitive action. The audit should focus on areas in need of general improvement and methods to achieve practice goals of the group or within the organization.[58]

Clinical audit itself is not research, although it may generate research questions. Because an audit reveals epidemiological and demographic information about a clinical practice, the results may lead to publication of healthcare trends or results of a quality improvement process. In an era of increasing attention to patient confidentiality and ethical research practices, approval to conduct an audit may be required by an organization. This is especially true in the United States where academic centres and many healthcare organizations have institutional review boards to ensure the safety and confidentiality of patient information.

Future initiatives in healthcare quality

With the advent of high technology, the perception of quality has expanded to encompass the use and accessibility of electronic and computer-based devices in healthcare. Medical diagnosis, treatment and documentation have advanced in sophistication to a point where electronics are standard and necessary for patient care practices. Healthcare services, communication and reimbursement are expedited with the use of high technology. Individuals and organizations without internet access, electronic medical records, or access to innovative diagnostic/therapeutic devices may be viewed as 'behind the times'. Healthcare consumers have an increasing expectation, well-founded or not, that technology-based initiatives provide superior quality and better medical outcomes.

High technology in medical education

The use of technology has fundamentally altered the format of medical education. Computers have changed the classroom environment and augmented the quality of medical presentations. Lectures now efficiently utilize multimedia resources with the ability to present complex content using sophisticated instructional formats. Internet-ready classrooms allow an educator to conduct a search of the literature and access clinical information in real-time.

Online, as opposed to live in-class lectures are available at many medical schools. In one study, students expended 50 minutes less time to complete an online lecture activity than the live lecture group, but demonstrated equal post-lecture knowledge.[59] Many studies have failed to demonstrate the superiority of internet-based or computer-assisted tutorials over the traditional lecture and textbook format.[60–63] Thus an 'electronic professor' does not replace the need for live interaction with medical educators. Like any instructional tool, electronic and computer-based programmes must be used in the right context, for the right group, and with the appropriate level of 'real-life' interaction.

Subjects with a high degree of visual-spatial complexity such as gross anatomy and histology have seen remarkable benefit from the growth of digital teaching tools. Three-dimensional views and electronically created images have assisted students in understanding anatomical and physiological relationships. Trainees are being exposed to new technologies from the classroom through the clinical

years. Teaching tools that did not exist just a few years ago are readily being incorporated into the educational environment.

New methods of medical education using simulation models are of increasing interest in reducing the incidence of procedural complications. In some studies, surgeons who received virtual reality simulator training for laproscopic procedures demonstrated significant improvement in skill performance over those without this training.[64,65] Other research has failed to demonstrate a difference in procedure time and patient discomfort between medical residents trained using a virtual reality-based procedural simulator and traditional bedside teaching techniques.[66] As the use of technology in diagnosis and treatment expands, so will the use of technology-based teaching tools in hopes of improving the quality of medical training.

In an effort to improve the efficiency and safety of patient care, hand-held Personal Digital Assistant (PDA) devices have become increasingly popular in medical practice and medical education. Some medical schools and residency programmes are providing trainees with these devices pre-programmed with educational tools and reference databases. PDAs have demonstrated benefit in reducing adverse medical events and improving the accuracy of medical documentation. Data is most supportive in the reduction of medication errors and identification of medication side effects.[67,68]

Because PDAs now have wireless and Internet access capability, the potential for remote-site electronic access to a central patient care database is being utilized at some institutions. This access can be especially useful for the geriatric medicine practitioner performing house calls, nursing home care and rural community-based care. These sites traditionally have limited access to electronic resources. Several institutions within the United States, including the VAMC system, have employed technologies that allow practitioners to use portable devices for remote access to patient information. Patient confidentiality has been addressed through the use of encryption programs that prevent unauthorized access by wireless users.

PDA programs can be used to track and store patient information. This is especially useful in the immediate and accurate retrieval of patient during after hours, off site and telephone consultation with patients and other medical providers. The applications to patient safety are of growing importance in the quality improvement process at all sites of care. The use PDAs and other portable electronic equipment will continue to grow as the demand for immediate and accurate medical information increases.

Electronic medical records

Electronic documentation of patient information is also of increasing importance in the delivery of quality medical care. The hospital setting currently makes greatest use of electronic records given the volume of information that must be collected and shared among medical practitioners. Whether data is entered electronically by practitioners or accessed in a read-only format, the electronic medical record (EMR) facilitates communication and access to information. Electronic charting has been shown to reduce documentation time and to improve the accuracy of assigning diagnostic codes.[69] The use of computer technology in patient management has repeatedly been associated with a reduction in the frequency of many types of medical errors.[70]

Many electronic record systems operate via an internet-based access system that allows users to enter and access data through any internet-ready computer. Other institutions use onsite computer systems that require users to access data through terminals or workstations networked for this purpose. This system limits access but is potentially a more secure means of maintaining patient confidentiality.

The VAMC in the United States exclusively uses an EMR. This computerized patient record system (CPRS) is the largest EMR in the world. All medical orders, laboratory tests, medical progress notes, medications and other data are entered and viewed electronically by all medical providers. The system can be accessed remotely for those providers located off of the main medical campus. Alerts, prompts and pre-designed order sets have reduced the occurrence of medical errors and improved the efficiency of medical care within the VAMC system. Those countries with national healthcare systems or large health provider groups (such as the VAMC) may be at best advantage to use an all-electronic record system, given the need for a well-structured system to oversee the design and support this form of health information system.

Telemedicine

With the advancement of digital data transfer, the Internet and wireless-based technologies, rapid relay of visual and audio transmissions have led to the development of telemedicine programs between remote geographic locations. Videoconferencing has extensive educational and clinical applications for the healthcare systems. Training can be provided in real-time using interactive video technology that allows remote classrooms sites to see, hear and speak with the instructor. Telemedicine allows primary and specialty care providers to interact with patients and clinicians in geographically isolated or underserved segments of the population.

In a Singapore hospital pilot project, geriatric specialists conducted telerounds with two off-site homes for the elderly.[71] This project was considered a success and was viewed favourably by both patients and clinicians. Improving access to healthcare resources is an area of ongoing interest in the quality improvement process. As the technology

improves and hardware costs decline, telemedicine will become an increasingly popular means of providing a broader array of healthcare services to a larger segment of the patient population.

Conclusion

'Quality of care' has been defined as, 'the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge'. Quality in healthcare has become a priority as cost, volume and efficiency became critical issues in meeting the growing healthcare demands of the medical consumer. Over the past two decades, the interest in healthcare quality improvement has grown dramatically. Consumer groups, medical societies and healthcare organizations have actively promoted quality in healthcare. These national and international associations work within the healthcare framework and governmental regulations unique to each country to help meet consumer and regulatory demands for high-quality medical services.

Based on the established healthcare and payer system, each organization may address quality control quite differently. Healthcare facility accreditation is a common means of marking quality and promoting the excellence of an institution. Other groups may choose certification using established standards such as the ISO-9000 process. At the level of the individual provider, performance may be assessed through audit or comparison of practices to established clinical guidelines.

The TQM process is well suited for the complex healthcare environment. This method is used to critically evaluate not only medical treatments and techniques but also the process by which medicine is delivered to the healthcare consumer. Quality improvement may then involve change in practice on an individual level and change in operation on a larger scale that benefits a broader population. Using quality indicators and outcome measures that quantitatively and objectively measure care, outlying data can be used to alert the organization to quality control problems.

Geriatricians are in a unique position to influence the healthcare quality improvement process. Interdisciplinary care and TQM are already familiar practices for most medical practitioners. As medical directors, geriatricians have taken a leadership role in improving institutional and rehabilitation practices. The quality of care for the elderly has been enhanced through new initiatives such as ACE and GEMU models and home-care technologies. Using new technologies, electronic databases and internet resources, care for the older population stands to broaden in scope and sophistication in coming years. Geriatricians will continue to be strong advocates for care practices that improve the process and outcomes of medical care for a growing and ageing population.

Key points

- The process of standardizing healthcare quality has evolved over the last 100 years.
- The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has accredited hospitals and healthcare facilities for over 50 years.
- Continuous Quality Improvement, also known as Total Quality Management, is a team-based approach used to evaluate and institute system-wide changes.
- Database analysis and healthcare audit are two methods of evaluating quality on a population-based scale.
- The use of computers and electronic communication systems have improved medical efficiency and reduced medical errors.

Appendix 137.1 Healthcare quality organizations.

Abbreviation	Organization	Origin	Created
ACHS	Australian Council for Health Care Standards	Australia	1974
ACHSI	Australian Council on Healthcare Standards International	Australia	2005
ACS	American College of Surgeons	United States	1913
ACSQHC	Australian Commission on Safety and Quality in Health Care	Australia	2006
AGS	American Geriatrics Society	United States	1942
AHRQ	Agency for Healthcare Research and Quality	United States	1999
(AHCPR)	(Previously Agency for Healthcare Policy and Research)		(AHCPR 1989)
AMDA	American Medical Directors Association	United States	1978
ANZSGM	Australian and New Zealand Society for Geriatric	Australia	2006
(ASGM)	Medicine (ANZSGM)		1970s
(AGS)	(Previously: Australian Society for Geriatric Medicine, Australian Geriatrics Society, Australian Association of Gerontology)		1960s
BGS	British Geriatric Society	United Kingdom	1947
CAHPS	Consumer Assessment of Health Plans	United States	1999
CHAP	Catalan Hospital Accreditation Programme	Spain	1981
CHI	Commission for Health Improvement	United Kingdom	1999
CHKS	Caspe Healthcare Knowledge Systems	United Kingdom	1989
(HQS)	(Previously Health Quality Service & King's Fund		(HQS 1998)
(KFOA)	Organisational Audit)		(KFOA 1989)
CMS	Centers for Medicare and Medicaid Services	United States	2001
(HCFA)	(Previously Health Care Financing Administration)		(HCFA 1977)
CQC	Care Quality Commission	England	2009
EFQM	European Foundation for Quality Management	Europe	1988
HC	Healthcare Commission	England	2004
HIW	Healthcare Inspectorate Wales	Wales	2004
IEC	International Electrotechnical Commission	United States	1906
IOM	Institute of Medicine	United States	1970
ISA	International Federation of the National Standardizing Association	Europe	1926
ISO	International Organization for Standardization	United Kingdom	1947
ISQua	The International Society for Quality in Health Care	Australia	1985
JCAH	Joint Commission on Accreditation of Hospitals	United States	1951
JCAHO	Joint Commission on Accreditation of Healthcare Organizations	United States	1987
NCQA	National Committee for Quality Assurance	United States	1990
NHS	National Health Services	United Kingdom	1948
RQIA	The Regulation and Quality Improvement Authority	Northern Ireland	2003
SCRC	Scottish Commission for the Regulation of Care	Scotland	2001
USPSTP	U.S. Preventive Services Task Force	United States	1984
VAMC	Department of Veterans Affairs Medical Centers	United States	1989
(VA)	(Previously Veterans Administration)		(VA 1930)

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CHAPTER 138

Clinical audit of healthcare

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> In order to work out how to improve we need to measure and understand exactly what we do.
> Making data on how well we are doing widely available to staff, patients and the public will help us understand variation and best practice and focus on improvement.
>
> Lord Darzi, *High Quality Care for All*, Department of Health, 2008.[1]

> At present, PROMs [patient reported outcome measures], other outcome measures, patient experience surveys and national clinical audit are not used widely enough. We will expand their validity, collection and use.
>
> *Equity and excellence: Liberating the NHS*, Department of Health, 2010.[2]

Definition

The Healthcare Quality Improvement Partnership (HQIP) in its *Local clinical audit: handbook for physicians* describes clinical audit as 'an approach to quality improvement based on clinical data collected by clinicians, to support the work of clinicians in improving the quality of care for patients.

Clinical audit is, first and foremost, a professional and clinical tool, not a management or regulatory tool. The General Medical Council (GMC) guidance requires all doctors to seek to improve the quality of care. Clinical audit provides a method for achieving such improvement'.[3]

Clinical audit has many definitions. One definition, internationally recognized and endorsed by the HQIP, comes from the *Principles of Best Practice in Clinical Audit*.[4]

> Clinical audit is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, process and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery.

The following chapter will expand on the components of this definition.

Background

Clinical audit and quality of healthcare

Professor Avedis Donabedian introduced the modern era of clinical audit with his seminal works in the 1960s–1980s.[5,6] He introduced a rigorous approach to improving quality in healthcare and developed the concept of measuring structure (what is needed to provide a good service), process (what is done to provide a good service) and outcome (what is expected of a good service) as key elements to evaluating quality of care. In the 1980s Royal Colleges were promoting medical audit as part of good professional practice. Over time, medical audit became clinical audit, recognizing that care is a multidisciplinary process, but audit remained a local activity with modest impact on the service.

In 1997, the new Labour Government introduced a sea change in the role of quality management in the NHS with the White Papers, *The new NHS; modern and dependable*, and *A first-class service: quality in the new NHS*. Quality of care was no longer to be the preserve of individual professionalism but became a matter of management responsibility. The government sought to improve the quality of healthcare by:

- Continual improvement in the overall standards of clinical care;
- Reducing unacceptable variations in clinical practice;
- The best use of resources so that patients receive the greatest benefit.

These aims were to be achieved by:

- Setting, delivering and monitoring quality standards;

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

• Making quality of care a management responsibility rather than just a professional commitment.

To execute these changes the government established bodies and programmes as indicated in Table 138.1.

In 2008, the government White Paper, *High Quality Care for All*, authored by Lord Darzi, built on the undoubted success of bodies such as the National Institute for Health and Clinical Excellence (NICE) and the Healthcare Commission in setting standards, monitoring standards and laying the foundation for improved patient care. The White Paper re-emphasized the importance of measuring performance, benchmarking and the use of data to drive change.[1]

In 2010 the White Paper, *Equity and excellence: Liberating the NHS*, provided the new Coalition Government vision for how the changes introduced in 1998 and reinforced by Lord Darzi could be developed further. The role of national audit was strongly endorsed with two particular changes of emphasis:[2]

1 The need to measure outcomes.

Organizational process targets would be downgraded and the emphasis would be on measures of clinical performance that are directly linked the improved health outcomes.

2 The need to embrace the patient perspective of healthcare.

The patient perspective would be incorporated increasingly into measurements of healthcare building on the use of patient satisfaction, patient reported experience measures and patient reported outcome measures.

Quality of healthcare can be broken down into 'domains'. Donabedian proposed two domains: technical quality of care and interpersonal quality of care. More recently the Institute of Health Improvement have proposed widening the concept to include six domains, namely: safety, effectiveness, patient centredness, timeliness, efficiency and equity.[7] Lord Darzi in *High Quality Care for All* emphasizes the importance of safety, effectiveness and the patient experience.[1]

Table 138.1 National developments to implement the quality agenda in healthcare–1997.

Setting standards
• National Institute of Clinical Excellence (NICE)
• National Service Frameworks (NSFs)
• National Clinical Governance Support Team (NCGST)
Delivering improvements in care
• Modernization Agency
• National Information Strategy
Monitoring standards
• Commission for Health Improvement (CHI)
• Performance Frameworks
• Patient Councils

National clinical audit

National audits have demonstrated over time how clinical audit can provide valuable information to address these domains of quality and contribute to improved service provision and patient care. National clinical audits, such as that of stroke[8] and myocardial infarction[9] have demonstrated the great variation in care in hospitals around the country as well as the dramatic changes and improvements in practice that have occurred over time. Data from such audits have had a significant impact on the formulation of national policy for developing services as well as providing local teams with invaluable data with which to seek improvements in care at a local level.

In addition to contributing to improving healthcare, national clinical audits serve other roles including providing a basis for research, education and revalidation.

Local clinical audit

Local clinical audit, while being routinely incorporated into the work requirements of trained doctors and doctors in training, has struggled to maximize its potential. In 2008 the Healthcare Quality Improvement Partnership was commissioned by the Department of Health to not only manage the national clinical audit programme, but also to re-invigorate local audit. The Partnership has initiated many projects to enhance local audit and has provided a much needed champion for all those involved in local audit.

Within the medical specialities, specialist societies have advanced their commitment to clinical audit, seeking to coordinate work, and provide web-based data collection systems to facilitate multisite local audit. Societies such as the British Thoracic Society have been in the vanguard of these developments. Such approaches will help all clinicians maximize the use of local clinical audit for the benefit of patients.

The audit cycle

Planning an audit

Identifying what is to be reviewed

It is sensible, for pragmatic reasons and on the basis of the research evidence relating to effective clinical audit, to focus on topics where there is a perceived inadequacy or variation in patient care or service provision. Professionals with specialized areas of interest may wish to perform an audit of local practice. Audit may be used as part of the clinical governance mechanism to explore aspects of care where there are concerns over the quality of care or where there have been significant numbers of complaints.

The value of an audit can be enhanced if the topic to be evaluated is important to several or many sites. It may be

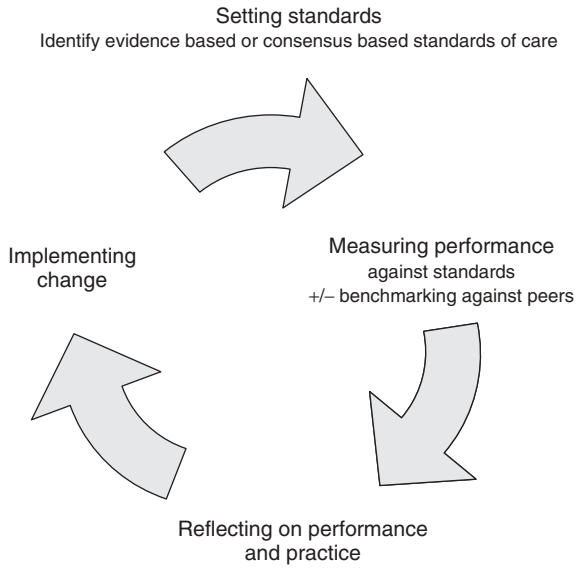

Figure 138.1 The audit cycle.

possible, either on a regional basis or via a specialist society, to coordinate the audit over a number of sites so that the data can be used to 'benchmark' local performance against that achieved by peers elsewhere in the country.

Commitment to audit

The recommendations of the Bristol Inquiry emphasized the importance of clinical audit within the system of local monitoring of performance and the need for trusts to fully support such activity – including access to time, facilities, advice and expertise.[10] These recommendations, welcomed by the government, echo the findings of systematic review, that clinical audit will only be successful if it is adequately resourced and it becomes part of routine practice.

Commitment is not just a clinical matter. It is essential that healthcare organizations as a whole seriously embrace these recommendations so that when results are available clinicians and managers are both willing to respond and jointly plan appropriate changes.

The planning phase needs to look ahead to how the conclusions will be used. This ranges from the need to include variables that allow for useful interpretation of the results as well as quality considerations to ensure the results are valid and reliable. The huge potential of audit for improving care can only be realized if the outcomes of each study are accepted as valid by all parties and thus utilized as the basis for reviewing and adapting practice.

Skills for carrying out audit

The infrastructure required includes access to skilled personnel (with dedicated time for the project) to carry out the work and systems to facilitate audit. Expertise is required in establishing a sound methodology for the work (see the following text) including an understanding of such issues as the size of population required for study, identifying relevant data for collection, the reliability and feasibility of data collection, data analysis, data presentation and implementation of change. Even apparently simple tasks such as setting out a questionnaire are in practice quite difficult. Poorly phrased or ambiguous questions result in data that cannot be interpreted. Therefore, most projects should be performed in conjunction with non-clinical staff with experience and expertise both in the technical aspects and in project management. They need support from professional healthcare workers to ensure the clinical acceptability and credibility and hence the validity of the study. At a local level, clinical teams should, therefore, work with clinical audit departments to ensure issues of methodology and project management are properly addressed. For national clinical audit significant investment in such audit infrastructure is required to ensure effective project delivery.

A multidisciplinary team is required that can effectively oversee and provide advice on the planning, carrying out and dissemination of the results of audit work. The group should include user involvement.

Modern audit has been made possible by the widespread availability of computing systems. They include software that can facilitate data collection, code and encrypt patient identifiable data and do sophisticated analysis. Access to such resources and expertise will enhance the audit process.

Patient and user input

Health services exist to serve the public and any assessment of care quality should include patient and users as full partners at all stages of the assessment process. Feedback from service users may shed a useful light on where services are inadequate, and also on the users' perspective of what is important as opposed to the views of management and professionals. Kelson has provided useful advice as to how user involvement can be achieved.[11]

As well as involving patients in the setting up and running of audits it is increasingly important to ensure that audit evaluates care from the perspective of the patient or user.[12,13] The patient perspective can be measured in terms of:

1 Patient satisfaction measures.

These measures provide a global assessment of the healthcare received [process] or the outcomes of care [outcomes] from the patient perspective. Such measures are helpful in monitoring trends but are very non-specific and provide no insight into the cause of any inadequacy of care.

2 Patient reported experience measures (PREMs).

These gather more specific feedback from patients with regard to the process of care received. These do provide an insight into where deficiencies in service provision lie from the patient perspective. Such measures are useful for assessing care for patients with chronic conditions.

3 Patient reported outcome measures (PROMs).

Such measures are currently much in vogue. There is a disease-specific component and a global component that measure the patient's perception of their health status following an intervention. Currently such measures are developed and in use in the NHS for surgical procedures, for example hip surgery, varicose veins surgery, hernia repair and cataract surgery. PROMs for more medical conditions are in the process of being developed.

Determining standards

As indicated in Figure 138.1, explicit standards of best practice must be established against which to audit. The important first step is to establish a statement or statements of the level of practice against which healthcare is to be assessed. There are two approaches: (1) define a gold standard and assess against that absolute target, or (2) collect comparative data and assess relative performance against the benchmark created by what one's peers are doing. In theory, the gold standard is preferred but often the evidence needed to set that standard is lacking. Furthermore, gold standards can rarely command 100% compliance, for example the Coronary Heart Disease NSF (National Service Framework) target for 30 minutes 'door to needle' for thrombolysis was set at 75% to allow, for example, for those where diagnosis was delayed.[9]

Evidence-based standards

Where possible, such statements of best practice should be derived from evidence-based research. The process calls for careful attention to literature searching, critical appraisal and peer review. The methods used by such bodies as the Cochrane Collaboration, the Scottish Intercollegiate Guideline Network (SIGN), and the National Institute for Health and Clinical Excellence (NICE) all ensure a high degree of credibility in the recommendations derived. Evidence-based audit standards can be determined from such recommendations.

Example: The NICE Clinical Guideline on 'Chronic Obstructive Pulmonary Disease' (COPD) has as an evidence-based recommendation that 'The presence of airflow obstruction should be confirmed by performing spirometry. All health professionals managing patients with COPD should have access to spirometry and be competent in the interpretation of the results'.[14] The audit criterion proposed to complement the recommendation is: 'Percentage of patients with a diagnosis of COPD who have had spirometry performed'.

The role of NICE is becoming increasingly important in not only developing guidelines but also in producing associated quality standards.

Consensus-based standards

Where it is not possible to obtain evidence-based standards consensus techniques should be used.[15] These will enable the best opinion of current health practice to be determined. The challenge in such a process is to ensure that there is no bias due to individual personalities or professions and to ensure that the views of all interested parties are included. Approaches include the following:

Consensus panels: the use of panels who receive expert advice and representation and who then formulate a statement of best practice.

Nominal group techniques: relevant parties are brought together to discuss recommendations. Chairing has to be skilled to ensure that all view points are heard and to ensure that a full range of options are considered. Voting is in a blinded fashion so that personal views are expressed.

Delphi exercises: postal questionnaires are sent to a large range of individuals with a relevant interest. Statements of practice are proposed and voted on. Recommendations are refined and recirculated so that the recommendations move toward a consensus of the views of the group.

Selection of gold standard

In practical terms, healthcare settings will need to determine what aspect of care they wish to audit. They will then need to seek the most appropriate standard(s) against which to audit, which has the authority of being derived from one of the approaches above.

Determining audit criteria

The Donabedian principle of measuring structure, process and outcome remains the basis for selecting the type of audit criteria.

Structure

Measures of the facilities and resources available to a healthcare setting will reflect the potential to provide high-quality care. It is difficult for staff to provide a high-quality service unless they have the resources to do it. Equally, it has to be recognized that high-class care is not guaranteed in premium facilities. Facilities have to be matched with staff who are provided with training and the expertise to carry out the appropriate care.

Example: For coronary heart disease, if a hospital does not have access to immediate coronary angiography it is not possible to provide the highest quality care for people with acute coronary syndromes.

Measures of 'structure' can include facilities, staffing levels, skill mix, access to training, standard use of protocols, mechanisms for advice and information for patients and relatives. Data relating to 'structure' are the easiest of the audit measures to obtain. Such data form the basis of accreditation schemes and systems of this type are widely used internationally and in some parts of the United Kingdom as an indication of service quality.

Process

Audit criteria of 'process' explicitly define key aspects of care that should be provided if high-quality care is to be achieved. Aspects of process measured may include the history, examination, investigation, treatment and follow-up care. The process may also include the involvement of carers. Processes of care need to be clearly defined to ensure reliable comparison between different sites and different data collection episodes.

Example: In stroke care, a swallow assessment is important as a process. The audit has to define what constitutes an appropriate swallow assessment and what detail within the records reliably reflects what was carried out. Process data may be collected retrospectively by reviewing a selected number of cases. Such an approach has significant problems in ensuring that there is no selection bias in the notes that are retrieved. A planned retrospective audit such as the National Sentinel Audit of Stroke[8] (assessing the care of 40 *consecutive* stroke patients in all hospitals in England, Wales and Northern Ireland) reduces the risk of bias. An alternative, but organizationally more challenging, approach is to obtain prospective data with data collection part of routine practice as in the Myocardial Infarction National Audit Project (MINAP).[9] In practice, measurement of process provides a useful reflection of whether care matches up with expected best practice. Data related to process can be more difficult to retrieve than measures of structure but tend to be easier to collect than outcome measures and have the added benefit that they are not dependent on case mix. Structure, process and outcome are all interrelated. Data from the National Stroke audit has demonstrated that settings where good structures are in place presage better processes of care and lead to better outcomes. It is rarely apparent, however, at the outset, which will be the most sensitive measures. Increasing clinical audit experience will help provide an indication of the structures and processes that are important in determining high-quality care. There are problems, however. If specific processes are identified as the markers for quality, departments and services wishing to be seen to provide high-quality care may concentrate purely on the selected process to the detriment of overall care.

Outcomes

Ideally, the quality of healthcare should be evaluated by the outcomes it achieves.

Example: For urinary incontinence, does appropriate assessment and treatment of patients result in a reduction in the prevalence of incontinence?

Outcomes may be recorded as outcome 'measures', for example prevalence of a condition or death at 30 days, or as an outcome 'indicator', for example percentage of asthma patients given a steroid inhaler on discharge. The latter is a process proxy that is linked to risk of readmission but is not in itself an outcome. Outcome 'measures' can be difficult to utilize. Consideration needs to be given as to whether an outcome 'measure' is a true measure or a surrogate measure. For the treatment of osteoporosis, reduced fracture rate is more important than increased bone density, although the latter is easier to measure. When measuring outcomes great care needs to be given to: the definition of terms, clarifying numerator and denominator populations, case mix and sample size (see 'Collecting data' below).

Outcome 'indicators' provide an alternative to outcome 'measures' and have the potential advantage of being (1) measurable and (2) having face validity for those involved in treatment, that is, it is not surprising that giving out an effective therapy works. While it is important to determine whether outcome measures can be used, in practice it may be more pragmatic to use outcome indicators.

Whether 'measures' or 'indicators' are used, it is important to be clear from whose perspective the outcome is being considered; is it that of the professionals, the management, the patients, or the carers? For stroke, professionals may seek the best neurological recovery, the patient may seek the best functional recovery, and the management may seek the most cost-effective recovery, all of which will be measured in different ways. The patient perspective is increasingly important[2] and may be recorded as patient satisfaction, experience or outcome.[12,13]

Outcomes provide data that most directly demonstrate progress with improving healthcare. In the future health outcomes will be increasingly sought as a measure of healthcare performance.[2] However, there are pitfalls in using data in this way that need to be carefully borne in mind. League tables relying on outcome measures have generated some bizarrely anomalous results and are mistrusted. One District General Hospital which was a beacon site for stroke care had a very high stroke death rate (Hospital Standardized Mortality Rate (SMR) was approximately 120) but the district SMR was only 94. As a beacon site, the hospital was keeping all patients with transient ischaemic attacks and mild strokes out of hospital or in intermediate

Table 138.2 Considerations with regard to clinical audit data collection.

Defining terms
Defining populations
Case mix adjustment
Sampling
Data sources
Define data analysis
Consent and confidentiality
Piloting

care facilities – thus the hospital SMR was based upon a different population compared with other hospitals. If public scrutiny of outcome measures is to occur, great care will be required to adjust for the potential confounding factors.

Collecting data

Issues that need to be considered are shown in Table 138.2.

Defining terms

Consistency in data collection requires accurate definition of terms throughout the audit proforma.

In the National Sentinel Stroke Audit (organizational)[16] for example, patients should be managed in a 'stroke unit' but in the absence of an accurate definition of such a unit, responses to audit questions are unlikely to be consistent.

All patients with suspected stroke should have brain imaging and in the majority of cases this needs to be conducted rapidly – within 24 hours after admission. However, if the patient is moribund, this may not be appropriate and thus in collecting data for audit purposes, a 'No but ... ' option will allow the case to be excluded because the standard is not applicable.

The appropriate data to collect from notes must be clear. If a blood pressure measurement is required during a hospital stay, is it the first recorded measure, the mean, or a measure at some specific time point that is required? How does the data collector deal with a comment written in the notes such as 'blood pressure normal' rather than a specific measure?

It is essential that these issues are clearly addressed or there will be considerable variability in the audit data collected from different sites and between different auditors. Advice sheets or notes addressing these issues are extremely helpful to audit teams and should, where possible, be backed up with recourse to the audit developer to clarify specific issues if necessary.

The development of standardized, or national data sets, are also helpful as they establish key data to be collected and identify the problems that may arise in data collection.

Defining populations

Outcome measures are often expressed as prevalence rates.

Good healthcare for urinary incontinence should reduce the prevalence of incontinence. How will the population with urinary incontinence be defined, identified and measured (the numerator)? Is this the population within a ward, a hospital, a general practice list, a Primary Care Trust? Is the prevalence to be determined per 1000 population, per number entering a service or on a GP list (the denominator)? In making comparisons with other healthcare settings it will be important that both the numerator and denominator are comparable.

Again, clear advice to the auditing team from the audit developer is essential.

Case mix adjustment

Comparisons of outcomes between settings will require case mix adjustment.

When planning an audit, the ways in which data will be presented, and to whom, should suggest what objections are likely to be raised to the results. Usually, these will be because a particular confounding factor has not been considered. Adding the appropriate extra variables increases the work of the audit but ensures that the results/comparisons are accepted as valid.

Example: For urinary incontinence when comparing between care in different nursing homes, it will be important to be aware of the physical dependency and cognitive function of people whose care is being assessed. Differences in the numbers of people with dementia and with relevant physical disability such as stroke, will have an important impact on the prevalence and management of continence.

There are many potential factors to take into consideration in case mix adjustment. In practical terms, it is sensible to collect only case mix data that are relevant to the planned presentation and use of the data.

Sampling

The sample size must be determined to ensure that meaningful results are obtained. Numbers will vary according to the measure being audited. These are statistical considerations that will not be described in detail, but intended to ensure that the results of an audit are robust enough to justify changing care practice and are not simply chance findings.

In the National Sentinel Audit of Stroke (clinical),[8] each site retrospectively reviewed a minimum of 20 and a maximum of 60 case notes of patients admitted between 1 April 2008 and 30 June 2008 with a primary diagnosis of stroke. If analysed alone, it would be hard to reach many

conclusions but when compared with 11 300+ cases from other hospitals, the statistical power is greatly increased.

For outcome measures, a power calculation is required depending on the degree of change expected. If the desire is to see whether the management of osteoporosis is satisfactory using fractured femur as an outcome measure, many thousands of cases will need to be studied. If the outcome measure is the appropriate prescribing of bisphosphonates to prevent osteoporosis, meaningful results can be obtained with small numbers of subjects and can be achieved within hospital departments or general practices.

It may not be possible or practical to obtain all records and some method of randomization may be required. This may be achieved by collecting all cases over a limited period of time – or by the use of random numbers. Care must be taken to ensure that all randomly identified cases are obtained so that no systematic bias influences the findings. It may, for example, prove difficult to obtain notes when a person has died. Exclusion of such patients may have an important bearing on the evaluation of quality of care.

Data sources

Clinical data are usually obtained from patient records following identification of eligible cases often via coding systems in healthcare organizations, such as Hospital Episode Statistics (HES) in England which capture ICD-10 (diagnosis) and OPCS-4 (procedures and interventions) information, or 'Read Codes' in General Practice.

The difficulty in obtaining reliable data retrospectively from patient records is familiar to most healthcare professionals. Unless there has been a predetermined data set incorporated into the records systems, there will be inherent difficulties in obtaining reliable data. Processes and outcomes of care may occur without being recorded. The data required may not be readily accessible. Different departments and practices use different data record systems.

In order to increase the likelihood of reliable data collection, it is advisable to limit the numbers of items to be collected and to give careful consideration to what is most reliably available and important in the record systems to be reviewed.

For the future, standardized data collection systems in routine practice, for example standardized admission clerking sheets or IT systems, will simplify data collection. Furthermore, the goal should be to incorporate required audit data items into routine collection so that prospective real-time audit data collection becomes possible.

Consent and confidentiality

Issues of consent and confidentiality are complex.

The General Medical Council[17] makes it very clear that patients have a right to have their medical data handled confidentially, but also makes it clear that doctors must keep good records and should actively evaluate the services they deliver. Therefore local audit, that is the evaluation of care quality within the clinician team, is considered a part of direct medical care and does not require specific patient consent nor is it subject to formal ethical approval. Whilst clinical audit does not require formal ethical approval, it must nevertheless be conducted within an ethical framework which means abiding by the principles of the Data Protection Act.

The Data Protection Act in the United Kingdom and parallel European legislation provide important safeguards to individuals to ensure that any data (paper or electronic) held on them is handled in a responsible manner that reflects their wishes.

Many patients have care from different parts of the healthcare system, for example diagnosis of a tumour in a district hospital followed by referral to a tertiary centre for radiotherapy. Within cancer networks both secondary and tertiary units form part of the cancer team, such that when evaluating the effectiveness of care both parts are important. The concept of the 'domain of care' or 'care across interfaces' is more useful than simply considering the institution. While it is permissible to collect data from the records of identified individuals, it is not permissible to identify those individuals in any of the resulting reports or analyses without the specific consent of that individual. A guidance document from the HQIP provides useful information with regard to the Data Protection Act and related issues.[18]

An important feature in the data protection legislation is that patients receiving care should be made aware of how their data are to be used. It has not been routine practice in the United Kingdom to provide leaflets for patients about the use of their data but this is now increasingly required along with information as to how individuals can 'opt out' of allowing their data to be used. The National Diabetes Audit was one of the first to provide such information and to develop a process to manage those patients who chose to opt out.[19]

Many audit studies would like to combine data from more than one unit and thus require local units to submit data to a central analysis system. This can only be done under three very specific conditions:

- If the locally collected data are fully anonymized, that is, all identifiers such as name, date of birth, post code, are removed then the data may be transmitted to a centre to be aggregated and analysed.
- If some of the identifiers are retained within the data but encrypted or 'pseudonymized' in such a way that no one in the central team can 'read' the original, then the data are treated as 'effectively anonymized'. This may be useful if it

is required at a later stage to link the data on an individual across more than one database – an activity that can be performed within the machines via the encrypted identifiers, and without needing central staff to break the code.

- If specific consent has been obtained from each patient to permit the transmission and use of their data.

It is a requirement for every NHS organization to have a Caldicott Guardian.[20] This is normally a senior health professional who oversees all procedures affecting access to person-identifiable health data. Anyone establishing an audit that requires data to be shared beyond the 'clinical domain' should check with the Caldicott Guardian to ensure that all necessary precautions have been taken. Those collecting data must also consider other aspects of confidentiality such as the need to store data files in a secure filing cabinet or on a secure computer, and that data protection duties extend not only to the rights of the patient but also to the rights of the clinicians delivering the services.

Piloting

It is essential to pilot an audit project to test the method for identifying cases, along with the feasibility of collecting information from records and entering them to the data-collection tool, be it paper or electronic. Testing a 10% sample in a pilot phase will provide an opportunity to assess inter-rater reliability by asking more than one person to collect and submit data from the same sample, as well as checking the data to see if they present a reasonable reflection of practice.

An evaluation of the pilot phase should lead to refinements of the methodology, data collection tools and supporting documents prior to the full audit, as appropriate.

Dissemination and change

The benefits of clinical audit as a quality improvement tool can only be realized if there is a mechanism for stimulating change to improve future care where change is required. Knowledge translation (KT), achieving the translation of research evidence into practice is an increasingly well-researched area of which audit and feedback forms just a portion. Unfortunately, the evidence for the impact of audit and feedback alone in promoting change shows only a small effect and needs to be supplemented by other KT techniques to achieve a lasting impact.[21] Certainly the very act of performing the audit serves a function in raising awareness of the subject under study, and any working group involved in putting together the audit can act as champions (see below) for the audit.

It is, in general terms, impossible to over-communicate during the period of the audit to maximize awareness. An integrated approach to communication as the audit progresses is important to keep auditors engaged, deal with problems along the way and keep the process alive. Once the results are available then they must be as widely distributed as possible, and in various forms, depending upon the intended audience. Generating an audit report is really only the first stage in the change process. Feedback to and engagement of clinical teams on the ground is important to begin the process.

Many different techniques have been used and researched to achieve change, such as mentorship and facilitation by an external 'change agent', peer and reminders (see Table 138.3). It is clear, however, that certain elements must be in place to maximize the impact of clinical audit as a tool for quality improvement as achieving change in a complex healthcare system (like the UK National Health Service) is difficult. Relevant factors appear to be: (1) motivation of key stakeholders to achieve the target for change; (2) instrumental, personal and interactive resources for change; (3) motivators outside the service, including the larger healthcare environment and government; and (4) opportunities for change – that is, how key stakeholders understand the change options. Unless these are addressed it is unlikely that improvements in practice, and hence the benefit of audit, will be realized. Likewise, the audit data must be perceived as valid and credible, be presented in a timely fashion to motivate change, be constructive, rather than destructive and complemented by both local ownership and a managerial commitment for change.[22]

Commitment

Clinical teams may accept the findings of an audit but be unable to improve care because they do not have the authority to make the required organizational or financial changes needed to facilitate this. Change therefore requires the active cooperation of both clinical and management teams in order to do this. Each audit project needs to ensure that the results will have sufficient credibility (data reliability, numbers, case mix) and that clinicians will embark on the discussions needed to create change. Planning should ensure that the right data are being collected, that the audit topic is considered important by the end users and that the aims are shared by all parts of the organization before data collection even begins.

The influence of a local champion in achieving change should not be neglected. Diffusion of innovation theory, using a social model[23] indicates that these individuals can have a marked impact upon the adoption of innovations. Published data, however, suggest that such champions have mixed effects on professional practice and that it is not always clear how their characteristics are defined or what they do that causes action.[24]

Table 138.3 Classification of quality improvement strategies (QIS) and their relative effectiveness.

Intervention	Level of effectiveness[†]
Clinician/patient driven QIS	
Evidence-based medicine	?
Clinical practice guidelines	+ + +
Care pathways	+
Guideline-based derivative tools that stipulate when certain actions should be taken in the longitudinal care of specific patient groups.	
Educational outreach	++
Upskilling of clinicians in their usual work environment by specially trained 'academic detailers' or content experts who may use written materials, case conferences, office or clinic visits, and practice reviews and feedback as educational tools.	
Local opinion leaders	++
Influential and respected clinicians working within local practice environments who encourage others to seek their opinions on best practice and emulate their practice routines.	
Audit and feedback	+ + +
Physician practice profiling	++
Internal peer comparisons and feedback based on relative utilization of tests, treatments and procedures, but in the absence of analysing concordance with evidence-based recommendations	
Peer case reviews	+
Review of individual cases of patient care provided by one clinician (or clinician group) by one or more peers not involved in the care of the original patients	
Clinical decision support systems	+ + +
Formal manual or computerized systems that prompt, remind and caution clinicians to do, or not do, certain things under specific clinical circumstances.	
Continuing medical education	-For most didactic + + + For small group interactive ? Depends on methods
Professional development and self-directed learning	
Deliberate processes of reflection, analysis of critical incidents encountered in personal practice, self-assessment and self-audlt, and personalized, self-directed learning based on identified gaps in knowledge and skills.	
Extended professional roles	Clinical pharmacists ++ Other disciplines?
Extension of professional roles of non-physician clinicians such as hospitalists, nurses, clinical pharmacists and others to include more of the tasks previously undertaken by other disciplines. Synonmys included 'task transfer' or 'task substitution' initiatives.	
Interdisciplinary collaboration and teamwork	?
Patient-mediated quality improvement strategies	+ + +
Chronic disease management	+ + +
Programmes intended to manage patients with one or more chronic diseases using systematic, multifaceted interventions comprising multidisciplinary care teams, patient self-management strategies, co-ordinated care teams with delivery system redesign, clinical information systems that track patient progress, care processes and outcomes, and evidence-based decision support.	
Specialty outreach programmes	+ + +
Delivery of medical specialist consultative services colocated with primary care and community care settings	

(*continued overleaf*)

Table 138.3 (*continued*).

Intervention	Level of effectiveness[†]
Multisite quality improvement collaborations The Institute of Healthcare Improvement in the USA, the National Health Service Modernization Agency in the UK and the National Institute of Clinical Studies in Australia have sponsored a number of multisite collaborations in hospital and primary care settings aimed at improving care for specific patient populations.	++
Manager/policy-maker driven QIS	+
Continuous quality improvement programmes Programmes aimed at continually improving care delivery aimed at providing a 'good' service that meets or exceeds patient expectations. Attributes of patient safety, convenience, timely access to care and efficiency of service delivery are the primary focus.	
System re-engineering (or business process redesign) Major structural changes, both clinical and managerial, across whole systems of care delivery aimed at improving care delivery and outcomes. Changes may relate to better use of information technology, measurement and reporting of performance; integration of services; realignment of payment policies; use of disease management strategies; quality and safety improvement programmes; and more efficient management structures.	Varies
Risk and safety management Systems that seek to minimize the frequency of preventable health care-related adverse events and reduce the medicolegal liability of individuals and organizations. Strategies include sentinel incident reporting, root cause analyses, risk registries and open disclosure policies.	?
Adjuvant models of care Models of care that obviate either the need for hospitalization or, if it is required, minimize the length of stay and reduce the need for readmission. Such strategies include formal discharge planning and facilitation procedures (with or without dedicated discharge coordinators), transitional care schemes (such as subacute care wards supervised by nurses for patients who require predischarge convalescent or rehabilitative care), acute care in the home programmes and community or home-based rehabilitation.	+
Public scorecards ad performance reports Many countries including the USA, UK, Canada and Australia have witnessed a growth in public release of hospital 'report cards' or 'scorecards', which, in some cases, have been used to rank hospitals according to performance.	
Pay for performance schemes Key attribute is a defined change in reimbursement to a clinical provider (individual clinician, clinician group or hospital) in direct response to change in one or more performance measures as a result of one or more practice innovations.	++ if directed to clinician groups
External accreditation and quality improvement Formal review of institutional performance by external accreditation agencies, which may or may not be coupled with external quality improvement organizations seeking to improve quality of care.	?
Clinical service networks Networks of like-minded institutions or groups of clinicians, which serve as agents of service change and improvement across large-area jurisdictions, with some acting as budget-holders and assuming purchaser–provider functions	+
Clinical governance Systematic coordination and promotion of activities that contribute to continuous improvement of quality of care: clinical audit; clinical risk management; patient/service user involvement; professional education and development; clinical effectiveness research and development; staff focus; use of information systems; and institutional clinical governance committees.	?

[†]Source: Reproduced from Scott I. What are the most effective strategies for improving quality and safety of health care? *Internal Medicine Journal* 2009;**39**:389–400, Table 2, with permission from Wiley-Blackwell.

Identifying the cause of problems

Where results of the audit show a divergence from accepted best practice, the reasons need to be investigated. Never presume that the observed divergence is the 'fault' of individuals, good staff may be handicapped by inadequate organization, poor facilities or resources available for service delivery, or the problem may relate to poor or outdated clinical practice. Once a cause has been identified, an action plan can be drawn up to address the problems.

Achieving change

Evidence suggests that there is considerable variation in the effectiveness of differing methods of achieving change. Most recent systematic reviews indicate that multifaceted intervention is not necessarily needed so long as one of the more successful targeted approaches is used. Details of the effectiveness of differing interventions are shown in Table 138.3. As noted above, simple feedback of results may not be enough and effects are most often small, although larger changes are noticed when the deviations from the accepted standards are large.[25,26] A recent meta-analysis building on the previous Cochrane review and using a theoretical framework first described in industry concluded that feedback needed to be frequent, non-punitive and individualized at the level of the individual practitioner and paired with goal setting for improvement in practice.[27] There are additionally data from a Cochrane review showing efficacy of printed educational materials in achieving positive change in professional behaviours and patient outcomes.[28]

The UK National Health Service's Institute for Innovation and Improvement (www.institute.nhs.uk) website contains a library of quality improvement and sustainability tools that are applicable to change management following audit and feedback which span every stage of the quality improvement cycle.

Sharing of data

Access to audit data has become an increasingly important issue. With the advent of clinical governance derived from the NHS White Paper *The new NHS: modern and dependable*,[1] audit has become very much part of the management process. Clinical data is increasingly required and used in monitoring the quality of services provided and the individual performance of clinicians. Audit data from multicentre projects are made available at local Hospital and Primary Care Trust level, to strategic health authorities and nationally to the Department of Health and to regulators such as the Care Quality Commission and form part of the annual quality report from each national health service institution. The National Clinical Audit Advisory Group in the UK National Health Service, established to advise the Department of Health with regard to national clinical audit, has recommended that all national clinical audits in England and Wales provide publicly accessible, institution identifiable audit results. Results therefore need to be presented in a manner that is understandable, with an accompanying commentary and will necessarily not include all the details of interest to clinicians. Such data will undoubtedly be used in revalidation of individual clinicians and in fitness to practice assessments as confidence in the quality of the data increases.

While this more open use of data is inevitable and will help drive the benefits of audit, it challenges those performing the audit process (managers and clinicians alike) to ensure that audit data are a true and fair reflection of the service and practice under review. This has implications for institutional support of clinical audit to ensure robust method, often such support at institutional level is lacking.

Re-audit and sustaining improvement

Cyclical re-audit must be carried out to 'close the loop'; to assess whether changes in service have resulted in improvement and to ensure that improvements are maintained. Ideally, with audit data incorporated into routine clinical care, prospective monitoring of performance can be maintained with minimal additional effort, but this is still a rare situation. Where recurrent cross-sectional audits are required, it is challenging for services to maintain continuous audit of one particular subject, particularly as priorities change over time.

Sustainability of change in clinical practice is also difficult and ideally the change required should fulfil the criteria specified by Rogers.[23] Such change should be compatible with existing routines; have relative advantage and not require extensive training; should be simple and customizable and its benefit should be observable to others. It is easy to see why the changes required in clinical practice, as judged by adherence to clinical standards or guidelines often do not meet many of these criteria and thus adoption is far more difficult. The Institute for Health Improvement (http://www.ihi.org/IHI/), based in Cambridge, Massachusetts, an internationally recognized body in the field of healthcare quality improvement, and the NHS Institute for Innovation and Improvement (www.institute.nhs/sustainability) both produce guidance, advice and toolkits for sustainability of change within clinical services, much freely available, which should aid the process.

In general practice other approaches have been adopted. The primary care information service (PRIMIS+) allows practitioners to compare anonymized data on practice performance. Although aimed primarily at enhancing data quality, it is hoped that ultimately patient care will also

benefit. The Quality Outcomes Framework, essentially items of service linked to payment, has led to much attention being given to key disease-related indicators. These financial benefits are impossible to replicate at the individual level in the secondary care setting in a social healthcare system without performance billing but the apparent success of these programmes would suggest that a lesson could be learnt which might be applied to hospitals.

In England and Wales, an annual quality report, mandated by the Care Quality Commission, the regulatory body for health and social care is currently under review, but contains elements relating to participation in and acting on results of clinical audit to establish clinical effectiveness. Additionally, clinical revalidation for the UK General Medical Council will require clinicians to produce evidence of participation as part of the process.

Conclusion

There is good evidence that clinical audit performed well can identify substandard care, can stimulate changes that improve care, and can confirm sustained improvement. Although the principles have been known for many years, the use of clinical audit has not been maximized by the professions and only relatively recently has the health service taken clinical audit seriously in order to inform quality assessments. The advent of new information technology should make data collection relatively easy but has yet to reach every clinical setting, particularly in nursing care homes, and as electronic patient records continue to roll out, albeit slowly, so will the opportunities for continuous quality improvement The adoption of the minimum data set, such as the Minimum Data Set – Resident Assessment Index (MDS-RAI) for care home residents, would be a major step forward for the UK. Such datasets have been adopted in many other countries, allowing standardized data to be collected for the benefit of many patients including the frailest in society. Clinicians need to take the opportunities that now exist to contribute to well-designed and targeted clinical audit programmes. Subjects should be chosen which are of priority importance locally and nationally and where there is evidence from other sources that current practice is suboptimal. Clinicians need to be involved with the intention of seeking sustained improvements in the service they provide and all clinicians should seek to ensure that their job specification includes time for audit. Healthcare management needs to be committed to the process, and this is likely to be the case given the drive towards outcomes assessment as the benchmark for clinical performance. This commitment needs to include the infrastructure, in terms of well-established audit departments whose direction is an integral part of the Trust strategy. There should be investment in systems for simplifying data recording and retrieval and there should be a commitment to routine audit data collection. Management also needs to demonstrate willingness to review and improve facilities, resources and staffing if such is required to improve services. Success breeds success. The realization that audit can induce change and improvement would strongly encourage commitment to the process.

Key points

- The clinical audit is a quality improvement tool.
- Clinical audits have demonstrated variances and inadequacies in healthcare.
- Audits can measure structure, processes or outcomes.

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CHAPTER 139

Carers and the role of the family

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> I was rung just before Christmas and was told that my mother [aged] 94 was ready for discharge that afternoon. I was also told that no one was available to help me until well after Christmas! I am 70 years old.
>
> Respondent to survey of carers' experiences of hospital discharge[1]

> Carers often have a deep insight into the condition of the person they are caring for … They need to be treated by professionals as ''Partners in Care''. [When carers are excluded, this can lead] to poorer outcomes for all and sadly on occasions [put] the person and their carers at risk.
>
> Chief Executive of voluntary organization[2]

Introduction

These opening statements highlight the importance of the role played by carers and families in achieving successful outcomes in geriatric medicine. Without carers' expert knowledge about the person for whom they care and the practical and emotional assistance that they provide, many older people receiving geriatric healthcare might otherwise need to remain in hospital or move into long-term care. Nevertheless, although professionals and policy-makers now possess much greater appreciation of the part played by carers than they did in the past, many carers and families continue to lack all the support that they need.

Over the past 30 years, a substantial literature on caring has developed and this chapter summarizes some of the key studies in the field that have especial relevance for clinicians working in geriatric medicine. It outlines some of the particular issues faced by those caring for an older person and some of the ways of identifying carers whose own health may be put at risk, either because of their own existing health problems or because their caring responsibilities have become too great. Examples of the types of support that carers find beneficial are given. However, it should be recognized that the chapter only provides a brief overview and there is an extensive literature on caring that goes beyond the material presented here.

Definitions of caring

Origins of the terms 'carer' and 'caregiver'

The Oxford English Dictionary reports that the first use of the term 'carer' to describe the unpaid work undertaken by people – generally women – looking after relatives or friends in need of support because of age, disability, or illness occurred in the late 1970s and early 1980s. In North America and Australasia, the term 'caregiver' is used more frequently than 'carer'. Both words share a similar etymological history in that their use can be dated from the time when increases in life expectancy and changes to the organization of systems of care for older people led to greater numbers of older people living at home and a reduction in the number of long-stay institutions. This coincided with wider recognition of the role played by women, in particular, in undertaking unpaid domestic work, often at the expense of their own opportunities for paid employment and for leisure time. Before long, it became clear that carers themselves comprised an extremely heterogeneous group and that this variation would influence their experiences of caring. For example, the terms 'women in the middle' and the 'sandwich generation'[3] were coined to describe the multiple responsibilities of women combining care of older parents or parents in law with other family and employment responsibilities. Other examples of attempts to differentiate between different types of carer include research looking at those caring for someone with a particular health problem, such as dementia,[4] stroke,[5] or Parkinson's disease,[6]

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the impact of kin relationships, such as being a daughter or spouse carer,[7,8] and the ways in which carers' demographic characteristics such as ethnicity[9–11] or sexuality[12] impact upon experiences of caring.

Conceptually, definitions of caring go beyond merely providing assistance with tasks such as shopping or bathing that people are unable to carry out independently by themselves.[13] Caring almost always takes place within pre-existing relationships and there are likely to be strong ties of affection or obligation[14,15] which strongly influence how older people and their carers respond to clinicians' recommendations about future care options, particularly when these involve a possible move into long-term care.

Distinctions between paid and unpaid caring

The appropriation of the term 'carer' or 'caregiver' to describe paid workers has meant that the prefix 'family' is increasingly added to the words carer or caregiver to differentiate between those with paid and unpaid roles. Even when family carers and those for whom they care are not biologically or legally related to each other, they often regard themselves as fictive kin, meaning that they may describe themselves as, for example, husband or wife, as if they had the actual relationship implied by the title. The term 'informal carer' was once used quite widely but family carers and organizations representing family carers criticized its failure to reflect the reality that so-called 'informal' carers provide the overwhelming majority of assistance to those in need of support. This is illustrated by secondary analysis of data on a representative sample of the older UK population which showed that 80% of those needing help with domestic tasks or activities of daily living such as washing or dressing received support only from members of their family, friends or neighbours with just 20% receiving help from any type of paid worker or volunteer.[16]

While this chapter is concerned with the support provided by family carers or caregivers, it should be recognized that blurring between paid and unpaid care does occur. For example, in the case of intergenerational transfers, older people may provide resources to adult children or grandchildren in return for care. Alternatively, a person originally employed to do domestic work may, over time, take on more and more caring tasks should their employer begin to require help with activities of daily living, such as washing and dressing. In instances such as this, the two may develop close ties that go beyond the traditional relationship between employer and employee. The introduction of 'cash for care' schemes through which family carers of older people receive a cash grant which can be used to pay for care in many countries in the more developed world has shifted the boundaries between the two further.[17]

Changes to the way' carer' and 'caring' are conceptualized

More recently, some commentators, especially those associated with the disability movement, have challenged the assumptions underpinning the words 'carer' or 'caring', criticizing its construction of people needing assistance in their daily lives as 'dependants' or 'recipients of care' and calling for new paradigms that reflect the realities of the reciprocities between carers and those for whom they provide support.[18,19] Thus, while 'carer' and 'caring' remain useful shorthand words to describe the range of support that is given in the context of relationships of kinship or affinity, they are not value free and may be interpreted in a variety of ways.

Legal frameworks

As Chapters 143–148 which describe different healthcare systems throughout the world show, variations in legislative and funding arrangements impact upon the type of assistance received by older people and their carers. In some countries, increasing recognition of the role played by carers has resulted in new legislative entitlements. These are not in themselves guarantees that carers will receive all the help that they need but they do influence the type of support that multidisciplinary geriatric teams can call upon when arranging care for their patients. In the UK, three pieces of legislation: the Carers (Recognition and Services) Act 1995; the Carers and Disabled Children Act 2000; and the Carers (Equal Opportunities) Act 2004 have given those defined as providing 'regular and substantial' care the rights to have their needs assessed and to receive services in their own right. In Australia, while there is no national legislation to protect carers, several states have introduced their own legislation, for example the South Australian Carers Recognition Act 2005. In Germany, the introduction of long-term care insurance (*Pflegeversicherung*) has improved the position of carers[20] while, in Finland, carers are entitled to cash benefits in return for a contractual agreement to provide a certain amount of care.[21] Carers may also have rights arising from employment or equalities legislation that protects them from discrimination arising from their status as carers. However, this picture is very variable and much may depend upon the extent to which family members are held legally responsible for the care of their older members and the existence of some policies which can actually penalize those who are providing care because the person for whom they care then loses his or her rights to support from statutory sources.[22]

Assessment of family carers

Even when there is no legal obligation to assess carers' needs, good practice dictates that geriatric assessments also

include an assessment of what support is provided by family carers and how they are managing. Carers' assessments need to identify, first, what support carers are providing and secondly, their feelings about how they are managing their caring role.

Typologies of caring

The gerontological and caregiving literature established some time ago[23,24] the nature of the inter-relationships between older people's needs, the extent and type of support they receive from family caregivers, and how its availability affects the need for support from 'formal' services such as home care (home health aides), sheltered accommodation and extra care housing (assisted living) and long-term care. In summary, it demonstrates that while friends and neighbours are likely to provide help with transportation, housework and shopping, it is rare for them to provide support with more intimate or personal activities, such as washing, bathing, or assistance in eating and drinking. Furthermore, where an older person has extensive support needs, for example if they are unable to be left alone for more than a few minutes (sometimes described as 'critical interval needs'),[25] it is generally only those carers who live in the same household as the person for whom they care or who live nearby who are able to provide this level of help. Most often, the majority of caring is undertaken by one person on his or her own (the primary carer), although 'secondary' carers may be involved. The most frequent example of a secondary carer in North American, European and Australasian societies is an adult daughter living apart from her parents but who supports one parent caring for the other. In Asian countries, the role of primary carer would traditionally be taken by the daughter in law. Where carers are providing help without any assistance from other family members or friends they are described as 'sole carers'.

It is important to establish exactly how much help carers provide on a daily basis and if other family or friends are providing any other assistance. As with comprehensive geriatric assessment (see Chapter 112) and assessment of residents in long-term care, carers' assessments need to be multidimensional in order to reflect the profound and far-reaching ways in which caring affects people's lives.

A theory that has been profoundly influential in the literature is the Stress Process Model[26] which distinguishes between *objective* stressors, that is, those factors that are attributable to the disease or disability in the person cared for, for example needing help to get washed or dressed, and *subjective* stressors, the extent to which the carer perceives these problems as causing them stress. The next subsections summarize some of the key areas that have been associated with carer stress. However, it is important to recognize that this process should not merely focus on deficits, such as the absence of social support, but should also take account of the strengths that carers may have,[27] such as their sense of determination or motivation.

Increased risk of psychological ill health

The effects of one person being almost wholly responsible for another person's care over time are considerable. While it is difficult to demonstrate direct causal relationships between caring and psychological health, there is strong evidence from both the United States (US) and the UK that some carers are in poorer psychological health than their age- and gender-matched counterparts in the general population.[28,29] Strikingly, the prevalence of psychological ill health among carers is associated with more intensive forms of caregiving, such as caring for a person in the same household and caring for more than 20 hours a week.[29]

An important message from this research is that clinicians should not assume that *all* family carers are at risk of psychological ill health but should aim to become more effective at identifying those family carers who are *at greater risk* of experiencing difficulties than others. In particular, clinicians need to be aware that while many family carers derive satisfaction and pride from their contribution, and wish to continue caring, there are circumstances in which the difficulties they face may outweigh the positive aspects of caring.

The impact of the cared-for person's health needs

Earlier chapters in this book have described the impact of long-term health problems such as dementia and other cognitive disorders (see Section 7), stroke (see Chapters 57 and 58), and Parkinson's disease (see Chapter 63). In addition to the way that these diseases impact on the lives of those older people directly affected by these conditions, research suggests that high levels of difficulty are reported among those caring for a person with dementia[30] or Parkinson's disease[6] and following a stroke.[31] Where the clinical picture also includes behavioural problems and aggression, then additional stressors may also be experienced.[30]

Physical health

As the opening quotation to this chapter showed, adult child or spousal caregivers of persons receiving geriatric healthcare are themselves likely to be older and at risk of age-associated health problems of their own. Poor physical health in carers does not necessarily result in poor psychological health but the deleterious effects of ill health seem to be most pronounced among older carers who may already be experiencing poor psychological health.[30]

Specific problems reported by carers include acquiring back pain from lifting or aggravating the pain of arthritis as

a result of helping someone else wash and dress. Caregiving has also been found to be associated with reduced functioning of the immune system,[32] meaning that carers may be more vulnerable to, or take longer to recover, from illness. However, despite high levels of physical frailty among many family caregivers, healthcare providers may actually have increased expectations about the tasks that they ask family caregivers to provide. There is some evidence that improved health technology has meant that many carers are undertaking tasks that in the past would have been undertaken by nurses or healthcare assistants.[33]

Financial aspects

Efforts have now been made to quantify the contribution made by family carers in terms of the costs of replacing family care with paid care and in the opportunity costs to carers as a result of their reduced opportunities for employment and leisure. For example, a report on dementia expenditure in the UK[34] concluded that dementia cost the UK economy around £19.7 billion per year (approx. US$30 billion). Of this, almost half could be attributed to the contribution made by family carers. On an individual level, carers may incur extra expenditure to pay for equipment, services, heating and clothing. In addition, they may give up paid employment, forego promotion prospects, or retire early. While women are still likely to be affected more severely than men, particularly in terms of being able to build up savings and a pension in retirement, this is an issue for both genders.[35]

Social support

Social isolation and loneliness are frequently reported by carers who may no longer have the time to meet up with family members and friends, or to pursue hobbies or other interests. Carers not only report feelings of loss and social isolation in their relationships with others, their relationship with the person for whom they care may also have altered. Others have argued that levels of *received* (or enacted) social support may not be as important as how carers *perceive* they are supported. Thus, good overall levels of perceived social support may be associated with increased carer well-being.[36] By contrast, if a carer does not feel supported, then he or she may express feelings of distress even if others are providing help.

Coping styles and strategies

Carers use a number of strategies to help them cope with caring[27,37] and these may influence the extent to which they seek and utilize support from others, including support from professionals and other family members. However, the exact nature of the relationship of coping styles to outcomes for carers and the person for whom they care is uncertain, not least because of uncertainties inherent in the disease process itself. Further, the use of coping strategies may reflect patterns developed over the life course which is why it can be valuable to find out how carers and those for whom they care have responded when faced with difficult life events at earlier times in their lives. It can also be helpful in enabling carers to identify the strengths that they bring to their caring experiences.

Screening measures for carers

A number of standardized measures have been developed to help identify problems faced by carers and summaries of the ones that have been used most extensively exist.[38,39] Unfortunately, the majority of these measures were developed for use in research and only a small number have been tested for their suitability in routine clinical settings where speed and ease of administration and scoring are important factors contributing to clinical utility. Examples of comparatively short screening measures designed to identify carer stress that have been psychometrically tested include the *Screen for Caregiver Burden* (SCB)[40] and the *Zarit Burden Interview* (ZBI),[41] also available in shorter 12 and 4-item versions.[42] Both were originally developed for caregivers of people with dementia but have been widely used with other types of carer. However, given that these measures were originally developed with ethnically homogenous, largely white, samples of carers, questions have been raised about their cross-cultural validity and the ethnocentrism of some of the ways in which they conceptualize caring.[43] Although Japanese versions of the ZBI[44] and Chinese versions of the SCB[45] exist, this remains an under-researched issue and it should also be acknowledged that some carers, whatever their ethnic and cultural background, would find the concept of caring as a 'burden' distasteful.

The suite of instruments, the Carers' Assessment of Managing Index (CAMI), Carers' Assessment of Difficulties Index (CADI), and the Carers' Assessment of Satisfactions Index (CASI)[46] were developed as a way of moving away from the concept of burden and incorporating a recognition that caring may bring satisfactions as well as difficulties. However, they are quite long, albeit in a format that is suitable for self-completion by carers who do not have literacy or sight problems prior to a clinical interview. Alternatively, the *Carers of Older People in Europe* (COPE)[47] is shorter, identifies positive as well as negative impacts of caregiving, and has been used in six European Union countries and in New Zealand.[48]

Although instruments such as these can identify carers who are experiencing difficulties with their caring roles, they are not designed to screen for psychological ill health. Clinicians may wish to supplement a screening measure about caring with one of the widely used instruments to

detect psychological ill health such as the *General Health Questionnaire* (GHQ)[49] or the *Center for Epidemiological Studies Depression Scale* (CES-D).[50] Alternatively, a measure of health-related quality of life (HRQoL), such as the *SF-36*[51] may also be valuable in identifying carers in need of additional support.

An important consideration for clinicians in geriatric healthcare settings is that carers' needs and QOL may change significantly if the person for whom they care has a progressive illness. Therefore, it is important to re-administer any standardized measures every 6–12 months in order to see if there have been any changes.

Arranging services to support carers

A number of services have been developed aimed at supporting carers, ranging from practical services designed to give carers a break from caring to psychoeducational interventions aimed at helping carers develop strategies to help them cope with different aspects of caring. Most of these will be delivered by other members of the multidisciplinary team including social workers, nurses, occupational therapists and psychologists. However, it can be helpful for clinicians to understand what these services are and why they have been found to be helpful.

In addition to the main interventions to support carers, described below, the interconnectedness of the lives of many carers and the older people for whom they care means that services ostensibly aimed at the older person, such as home care or hospital at home schemes may also be beneficial for carers, indicating that services for older people and services for carers need to be provided in tandem. Another example of the way in which services primarily intended for older people can bring benefits to their carers is the role of telecare (see Chapter 124). Assistive technologies may be particularly valued by carers who do not live in the same household as the person for whom they care.

Information

Satisfaction with information provision contributes to overall ratings of satisfaction among patients and carers. Despite this, the difficulty in accessing appropriate information at the right time is a constant theme within carer research. A Cochrane review of information provision for patients and carers following stroke concluded that while information improved patient and carer knowledge, it had no impact upon carer mood or satisfaction and that further work on the best way to provide information was needed.[52] Carers' accounts suggest that they value information that is timely and provided in both verbal and written forms. They also need a wide range of information, including information on the prognosis, symptoms and treatment for the person for whom they care but also about the services that might be available to them, including welfare benefits and information about financial and legal issues. A study of stroke survivors and their carers found that while carers were generally happy with the information they received about stroke, they were less happy with the provision of information on what community services would be available to them and information on legal and financial planning.[53] As with older people themselves (see Chapter 11), attention needs to be paid to using language that can be understood by a layperson and ensuring that any literacy or language needs on the part of carers are met. Organizations representing the interests of older people or carers have considerable experience in providing information and carers can be directed to the resources that they provide.

Studying recall is an important way of measuring the effectiveness of information provision but unfortunately more research on patients' rather than on carers' recall has been undertaken. However, good practice suggests that it is important to review the information provided to carers at a later date to see how much carers can recall about the information they have been given and whether it has been useful.

Carers' support groups

Support groups for carers generally fall into one of two types: the first is a time-limited intervention in which carers are offered training in how to deliver an aspect of care or in managing their caring roles. These will be described in more detail in the next section. The second offers an ongoing forum for carers to share their experiences and provide mutual support to each other. Long-term groups of this sort are also likely to provide a source of social support and social activities for their members. Although carers attending support groups generally evaluate them positively, not all carers are comfortable with the idea of meeting with others. In addition, substitute care arrangements may need to be made so that the carer is able to leave the person for whom they care.

Although carers' groups offering long-term support are generally open to anyone who wishes to attend, there are instances where attendance is restricted to carers sharing a certain characteristic, for example groups for people caring for someone with a specific disease. Another example is where carers share the same demographic characteristic such as being a member of a minority ethnic group[54] or being a lesbian, gay, bisexual or transgendered (LGBT) carer. In these instances, carers may be more likely to attend groups for specific types of carer because they feel reassured that that they will meet people in a similar position to themselves.

Carer and family support workers

One UK development that combines the role of information and support is that of the family support worker for stroke

patients and their families. These workers also liaise with other professionals. They have been positively evaluated by carers with one evaluation suggesting that they can result in demonstrable improvements in QOL for carers.[55]

Carer education and training

A number of studies have looked at the effectiveness of carer education and training programmes. Of these, the majority have looked at the impact of psychoeducational programmes designed to support carers of people with dementia, especially in terms of helping carers develop problem-solving techniques to deal with behavioural problems. Examples include training in cognitive behavioural therapy (CBT)[56] for carers of people with dementia, a psychoeducational programme to help deal with behavioural problems,[57] and a combined educational and support programme supplemented by follow-up telephone support.[58] When combined with cholinesterase inhibitor therapy in the person cared for, one study reported positive effects on the levels of depression among carers from quite moderate levels of input (five sessions of counselling plus ad hoc telephone support).[59] The use of telephone support highlights the potential to use alternative forms of delivery to enhance or replace interventions that are provided face to face.[60]

Positive results have also been reported from interventions designed to support carers of people with a stroke. A UK study looked at the effectiveness of a training programme for carers while the person for whom they cared received rehabilitation after a stroke.[61] At follow-up, carers who had undertaken the training programme had better psychosocial outcomes than the control group who had not. It also resulted in reduced costs of care.

Respite services

Respite is the term used to describe a range of services giving carers a break, ranging from one or two hours in the home to overnight care in care homes or specialist units. As with 'burden', the word respite does carry some negative connotations for the person cared for and the term 'break' is more neutral. As well as services that offer carers a regular break from caring, emergency services are also likely to be needed. Carers of older people are more likely to be sole carers and this means that if they become ill or if a crisis occurs, emergency respite care will be needed, ideally in the person's own home but more probably in the form of temporary admission to a care home.

A number of studies have looked at the impact of respite services but the results present a mixed and sometimes contradictory picture.[62] Partly, this is because the outcome measures used most often (changes in carers' psychological health and reductions in admissions to long-term care) may not be amenable to change from the provision of comparatively small amounts of help. Carers themselves rate respite services highly when they are felt to be of sufficient quality and meet the preferences of both themselves and the person for whom they care. Carers and service providers have different perspectives about what constitutes respite. This means that it is important that respite care is offered in a form that is meaningful to carers. The advent of 'cash for care' schemes may result in more choices for carers about how they find ways of taking a break from caring.

Service effectiveness

One difficulty in evaluating the effectiveness of services for carers has been the continuing variability in the quality of research. There has been little consistency in approaches to sampling and in the selection of outcome measures. Outside the United States, the number of controlled intervention studies remains comparatively low. This means that effectiveness is often judged on the basis of very moderate levels of service input, delivered in differing ways to differing groups of people using outcomes that can be quite intractable to change – such as carers' psychological health – rather than their QOL or their perceptions of benefit. Few studies have included measures of cost effectiveness. There are issues about the cross-national relevance from studies based upon service systems which may be very different. Furthermore, there is a need for new forms of evaluation that take account of the outcomes that are important to carers, not just to service providers, researchers, or policy-makers.

Role of clinicians in service utilization

Classically, models of service utilization have looked at the predisposing, enabling and illness-level determinants in explaining an individual's service utilization.[63] However, this approach has been criticized for failing to take account of carer characteristics, especially among certain types of carer, such as carers from minority ethnic groups[64] who are generally thought to be under-represented in services designed to support carers. An issue that is rarely reported in the literature but exists widely in everyday practice settings is the role played by professionals in helping carers to reach decisions about which services to use. There is now a much greater focus in medical education on enabling clinicians to acquire good skills in communicating with patients but this also needs to be extended to communicating with carers. Although there is now much greater societal recognition of the role of carers, knowledge about what services are available to support carers remains limited. This means that it tends only to be at times of crisis, such as hospital admission, that carers are asked to make important decisions about the sort of services they want and they are very often reliant upon professionals to explain what help is available

to them. This highlights the role of clinicians in signposting carers to potential sources of support and in liaising with other members of the multidisciplinary team. Follow-up and outpatient appointments provide a good opportunity to review the support provided to carers, as well as reviewing the treatment of the person for whom they care.

Discussion

Although this chapter has highlighted the diversity to be found among carers and the debates that exist about the effectiveness of different services to support them, a number of clear messages emerge. Many carers caring for older people using geriatric health services are themselves old and are providing considerable amounts of assistance. Although the majority of carers will not experience difficulties with their caring role, a substantial number will and this is usually influenced by the amount of care that they provide and the emotional context in which it is given. Interventions increasingly use a combination of methods and may be based upon the use of new technologies. The amount and type of care that will be required to sustain older people in the future is uncertain. Greater geographical and social mobility, changes in living arrangements with greater numbers of people living on their own and greater geographical distances between family members, may lead to changes in the way that care is provided. At the same time, new technologies offer new opportunities for people to remain in touch and to provide care at a distance. What is certain is that most family members continue to wish to care for their relatives. The challenge for services is in responding to the diversity of caregiving arrangements and in providing help that is acceptable to both carers and to those for whom they care.

Key points

- Carers provide the majority of support to older people needing help with their daily lives. Many of these are spouses with health problems of their own.
- It is possible to identify carers at greater risk of needing support themselves.
- Services need to be more focused upon the sort of help that carers themselves define as useful.

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CHAPTER 140

Nursing home care

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Introduction

Nursing home facilities are more unique than similar. The care of elderly persons in institutionalized settings varies by country and region and in societal and cultural factors. Nursing homes also rapidly evolved because the quality of nursing home care has become a growing concern everywhere and because residents are generally showing increasing levels of disability and require increasingly more complex treatments. However, this evolution relies more on empirical practice than research studies. Only 2% of the research into the elderly population concerns nursing home residents.[1]

Approaches to long-term care in various countries include chronic geriatric hospitals, short-stay rehabilitation centres, residential living centres and institutionalized skilled nursing homes. The nomenclature of a facility varies across settings, including 'nursing home' in the United States and 'care home' in the United Kingdom. A 'nursing home' in the USA may refer to a specialized centre for persons on ventilators, with acquired immunodeficiency syndrome or with dementia who need skilled nursing care. A 'care home' in the UK generally refers to a home registered under the Care Standards Act providing personal and residential care for older people and also includes homes that provide nursing care (nursing homes). Not only is the classification confusing, but also the public, and often the professional, view of nursing homes involves a number of misperceptions.

Misperception: most older adults will live for many years in a nursing home and eventually die there. Truth: fewer than 5% of older adults in USA and fewer than 10% in the UK and France reside in resident and nursing home settings.

Misperception: once a person enters a nursing home, they stay there for good. Truth: many older adults who enter a nursing home will recover and leave (short-stay residents), while fewer older adults will remain in a nursing home once admitted (long-stay residents). In France, half of the nursing home residents will also have a hospitalization every year.[1]

Misperception: nursing homes are warehouses for older persons with little or no stimulation: Truth: a good home provides a social environment that often is very comforting for older persons who may have been isolated in previous living environments.

Misperception: no one likes living in a nursing home. Truth: many residents prefer the reassurance of medical care, socialization and a safe environment and find the experience positive.

Facility demographics

In the USA, there are ~16 100 nursing homes with ~1.5 million residents. The number of nursing home beds decreased in the USA from 1999[2] to 2004[3] from 1.9 to 1.7 million beds, respectively. The average number of beds per facility rose to 108 from 105. The occupancy rate (number of residents divided by number of available beds) was 86%. However, the demographics of facilities vary by country. In France, the number of beds in nursing homes is about five times higher (about 10 000 nursing homes for 60 million inhabitants with a bed occupancy close to 97%).

Ownership of most nursing homes in the USA is by for-profit entities (61%); 31% operate as voluntary non-profit facilities and the remaining 8% are owned by governmental entities (Figure 140.1). Half of the nursing homes are public in France. In the USA some 56% of nursing homes are affiliated with other nursing homes in a chain ownership. These facilities account for 57% of all beds, 57% of all residents and 61% of all discharges. Most nursing homes (62%) are located in a metropolitan statistical area.[4] The distribution of nursing homes is uneven, with the midwestern and

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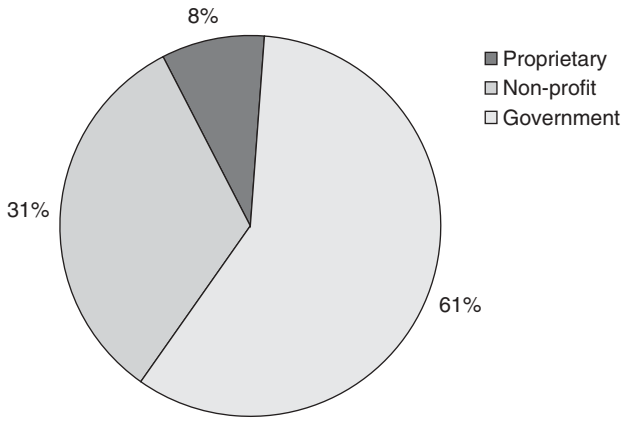

Figure 140.1 Percentage distribution of nursing home facilities by ownership: United States, 2004. Source: Jones AL, Dwyer LL, Bercovitz AR and Strahan GW. The National Nursing Home Survey: 2004 overview. National Center for Health Statistics. *Vital Health Stat* 2009;**13**(167):1–155.

southern US census regions having 34 and 32% of facilities and 32 and 33% of all beds, respectively.

The nursing home industry employs a large number of persons in various occupations (Figure 140.2). The rate of staffing does not appear to vary much by type of nursing home ownership. A major problem for patient care in nursing homes is the high staff turnover rate. A vacancy rate of 19% for nurses has been reported.[5] The turnover rate for nursing assistants has been reported to be as high as 93%.[6] These high vacancy rates disturb continuity and force continuous training of new personnel. This nursing home staff turnover impacts on the quality of care.[7]

Nursing home care is expensive. Residents in US nursing homes use several sources of payment (Figure 140.3). At admission, most residents reported private resources (42%) as a payment source, followed by Medicare (36%) and Medicaid, a means-tested governmental source in the USA (35%). However, during admission, residents using Medicare as a source of payment dropped to 13% of all current residents. Longer term residents reported private sources increasing to 66%, and those with Medicaid rose to 60%. The national cost of nursing home care was $53 billion in 1990 and was the fastest growing component of major healthcare expense in the national budget.[8] The projected cost for 2000 exceeded $140 billion and it may exceed $700 billion by 2030.[9]

These predictions of continued nursing home growth and expenditures are becoming modified by several societal changes. The proportion of Medicaid beneficiaries aged 65–74 years residing in nursing homes remained fairly constant at about 6% from 1999 to 2003, but the percentage of Medicaid recipients aged 85 years and older declined from 48 to 44% from 1999 to 2003. This does not reflect a decrease in Medicaid recipients, who increased from about 4.2 million in 1999 to 4.8 million in 2003.

The growth in community-based care alternatives to nursing homes, such as assisted living and other group residential options, has been suggested as one of the reasons for the shrinking nursing home population in the USA. However, there is considerable variability at the State level in the availability and provision of home- and community-based services to people with long-term care needs.[10] Because of the expense of nursing home care, several States have initiated programmes to favour home-based services financially. These trends will define the future number of nursing home beds required to care for the ageing population.

Nursing homes in other cultural settings differ considerably. For example, the Dutch experience demonstrates that among persons older than 65 years, ~20% had a short

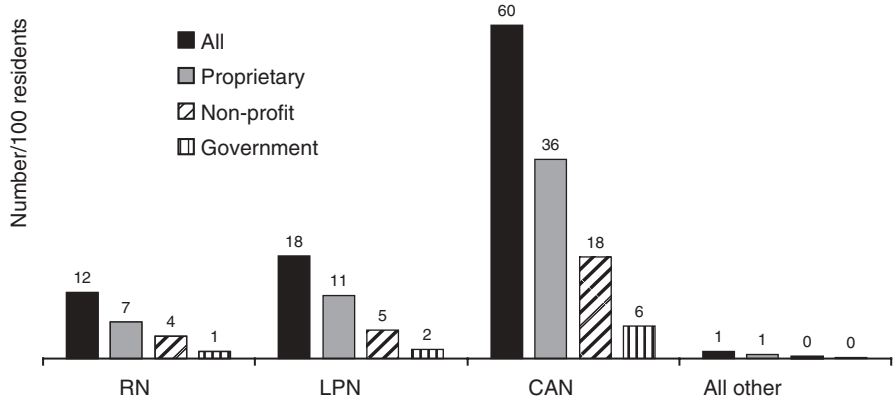

Figure 140.2 Number per 100 residents of full-time equivalent employees by occupational categories and selected nursing home characteristics: United States, 2004. CNA, certified nursing assistant; LPN, licensed practical nurse; RN, registered nurse. Source: Jones AL, Dwyer LL, Bercovitz AR and Strahan GW. The National Nursing Home Survey: 2004 overview. National Center for Health Statistics. *Vital Health Stat* 2009;**13**(167):1–155.

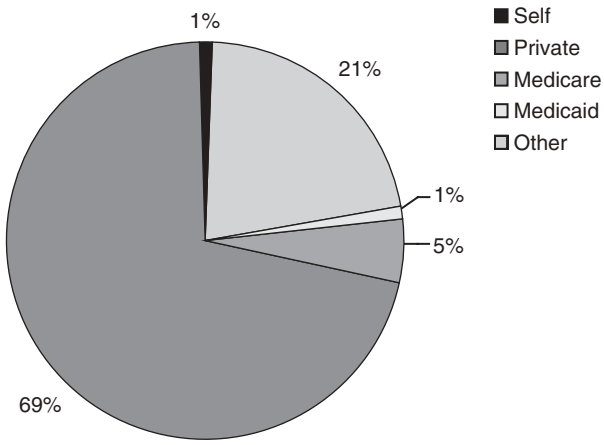

Figure 140.3 Nursing home payment source: long-term stay >90 days: United States, 2004. Source: Jones AL, Dwyer LL, Bercovitz AR and Strahan GW. The National Nursing Home Survey: 2004 overview. National Center for Health Statistics. *Vital Health Stat* 2009;**13**(167):1–155.

stay in an inpatient hospital department and 96% were discharged to their own home situation. Only 7% lived permanently in special institutions for chronic care, including residential care or nursing home care. Persons with physical disability or with progressive dementia, who have impaired activities of daily living (ADLs) and who need more complex continuing care beyond the range of home care services in a residential homes, are admitted to a nursing home. The number of nursing home beds is 3.6 per 1000 persons (in 2003), with a total of 330 nursing homes with ~26 000 beds designed primarily for persons with physical problems and 32 000 beds in psychogeriatric wards for persons with dementia. Nursing home care is covered by a mandatory national insurance system, the Exceptional Medical Expenses Act. In addition to the funds from this national insurance, income- and household-dependent out-of-pocket payments are obligatory for persons admitted to nursing homes.[11]

In the UK, the number of patients in private or voluntary homes rose from 18 200 in 1983 to 148 500 in 1994.[12] The number of institutional care beds for older persons doubled to 563 000 between 1980 and 1995. National Health Service beds accounted for less than 10% of the total in 1995 compared with 23% in 1980, while private and voluntary (not-for-profit) residential and nursing home beds increased to 76%.[13]

Persons in the UK receiving long-term care provided in care homes are required to meet financial means testing. Those who have assets, including the value of their homes (with some exceptions), above a limit (£23 250 in 2011) are required to pay the care home's fees in full. Those with assets below the limit make a co-payment that is usually less than the full fee. For those with the lowest income and assets, this payment may be met from Income Support, the UK's means-tested welfare benefit. Almost all older people who own their home would be required to meet care home fees in full. The same approach exists in France. The children are also constrained by a law obligating them to pay if the payment cannot be met by the resident.

Means testing dates back to 1948 in the UK and has changed little in the many years since then. However, the growing numbers of older persons and increasing home ownership have stressed the means test. Local public authorities are responsible for payment for long-term care for older persons who meet means test requirements, whether in a care home or in the person's own home. For care services delivered at home, the value of an older person's home is disregarded in determining how much he or she contributes. An older home owner is, therefore, likely to incur considerably more – and the public budget correspondingly less – of the cost of care in a residential setting than of the equivalent cost of care at home. The result is a financial incentive for public authorities to arrange for a home owner's care to be provided in an institution rather than in their own home. The financial incentive works in the opposite direction for older home owners themselves. Whether the likelihood of entry to a care home is increased or decreased by the level of an individual's economic resources would seem to depend on whether individual choice or the policy of the local public authority dominates.[14]

Resident demographics

In the USA, 43% of persons who were 65 years of age in 1990 will enter a nursing home in their lifetime. Of these, 55% will stay for at least one year and 21% will stay for five years or longer.[15] The percentage of retired patients who will pass through a nursing home during their lifetime is nearly double in some European countries.

Nursing home use is strongly associated with age, even after adjusting for disability. This suggests that the future need for nursing home care will increase as the population increases in life expectancy. By 2030, the need for nursing home beds in the USA is projected to increase to 5 million.[16,17]

Most nursing home admissions are for short-stay residents. About 2.5 million residents are discharged after an average length stay of 272 days. Long-stay residents remain in the nursing home for an average of 873 days.

In France, 70% of nursing home admissions come from hospital. Most of the time, the mean length of stay does not reflect the rapid turnover of a small proportion of the nursing home residents who died after a short stay while others stay for a longer period.[1] The changes in acuity and

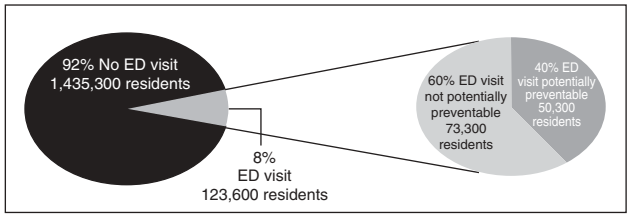

Figure 140.4 Percentage of nursing home residents with a potentially preventable emergency department (ED) visit in the past 90 days: United States, 2004. Source: CDC/NCHS, National Nursing Home Survey, 2004, http://www.cdc.gov/nchs/data/databriefs/db33.pdf (last accessed 7 November 2011).

dependence in most countries[18] result in increased needs such as care in the emergency department (Figure 140.4).[1,3]

Residents in nursing homes do not reflect the demographics of the general population. In the USA, most nursing home residents (71%) are female. Some 88% were aged 65 years and older and 45% were aged 85 years and older. The average length of time from admission for all nursing home residents was 835 days in 2004. The median length of time from admission was 463 days. Among nursing home residents aged 65 years and older, time from admission was less than 3 months for 19% of residents, 3 months to less than 1 year for 24% of residents and 1 year or more for 56% of residents. More than half of all nursing home residents were either totally dependent or required extensive assistance in bathing, dressing, toileting and transferring. In France, the mean age is about 84 years in a nursing home.

Nursing homes provide extensive services to residents. Almost all nursing homes reported providing nursing services (100%), medical services (97%) and personal care services that included ADLs (97%). Non-medical services most frequently offered by nursing homes include nutrition (99%), social services including assistance to residents and their families in handling social, environmental and emotional problems (98%) and physical therapy (97%). The least frequently offered services include hospice services (72%) and home health services (23%).

Nursing home regulation

In the USA, nursing homes are licensed by each state and require a certificate of need to operate. Each State regularly surveys nursing homes for compliance with State regulations. In addition, the Federal government contracts with each State to survey nursing homes for compliance with Federal regulations if the home receives payments from Medicare or Medicaid sources. Nearly all nursing homes (96%) have some form of certification. More than three-quarters of all facilities were certified by both Medicare and Medicaid. Only 4% of the 16 000 nursing homes were not certified.

Federal regulations are contained in two Congressional Acts, the Omnibus Budget Reconciliation Act of 1987 (OBRA '87) and the Balanced Budget Act of 1997 (BBA '97). OBRA '87 had a major impact on general nursing care, including the introduction of the Minimum Data Set (MDS), requirements for a Medical Director and the reduction in physical and chemical restraints. Regulations based on BBA '97 initiated the Prospective Payment System and consolidated billing. These Federal regulations have created standards of care in nursing facilities. The regulations resulting from OBRA '87 are divided into two parts. First, the law is stated. These statements are labelled by 'F-tags' and a number. An 'F-tag' is jargon for the actual law published in the Federal Register. Second, an interpretive guideline follows the regulation. The guidelines comprise the instructions used by surveyors to determine compliance with the law. Failure to comply with State or Federal regulations can result in fines or in decertifying the facility from participation in Federal programmes. A comparison of Federal quality-of-care indicators is published on the Internet and updated at intervals.

In the autumn of 2009, a new Minimum Data Set (MDS version 3.0) was implemented in the USA. Residents, families, providers, researchers and policymakers had expressed concerns about the reliability, validity and relevance of MDS 2.0. Some argued that because MDS 2.0 fails to include items that rely on direct resident interview, it fails to obtain critical information and effectively disenfranchises many residents from the assessment process. The new version MDS 3.0 was designed to improve the reliability, accuracy and usefulness of the MDS, to include the resident in the assessment process and to use standard protocols to evaluate nursing home residents.

A national testing of the MDS 3.0 was conducted in 71 community nursing homes in eight US States and in 19 Veterans' Administration nursing homes. The evaluation tested data reliability, the validity of new cognitive, depression and behaviour items, response rates for interview items, user satisfaction and feedback on changes and time to complete the assessment.

Improvements incorporated in MDS 3.0 produced a more efficient assessment with greater reliability and shorter completion time. A key component of MDS 3.0 was a focus on direct interviewing of the resident. For areas such as cognition, mood, preferences and pain, studies have repeatedly shown that staff or family impressions often fail to capture the resident's (or any adult's) real condition or preferences. Published measures of clinical conditions were incorporated into MDS 3.0 to increase validity. A direct-interview pain assessment, the Geriatric Pain Assessment,[19] uses resident self-report to obtain pain information. The pain severity items include the 0–10 scale, a recognized scale that is used in other settings, and the

verbal descriptor scale, which may be easier to answer for some residents with cognitive impairment. Depression is assessed using the PHQ-9 instrument.[20] The Brief Interview for Mental Status[21] assesses cognitive function. The Confusion Assessment Method[22] evaluates delirium, an exceptionally common problem in nursing home residents.

In the UK, nursing homes are required to report on their quality-of-care activities each year and are also regularly visited by Health Care Inspectorate personnel.

Medical care

Care of residents in a nursing home is overseen by a physician. Each nursing home is required to have a physician Medical Director, who oversees the quality-of-care in the facility. Each resident is seen by their physician, who either visits them in the facility or arranges for clinic visits. The frequency of visits is dictated by medical necessity, but cannot be less frequent than once every 30 days for the initial 3 months following admission or less than once every 60 days thereafter. Physician extenders or nurse practitioners may also see residents in a facility, but may not be used to meet this minimum standard. In France, each nursing home is supposed to be coordinated by a geriatrician on duty two days per week. He or she is mainly responsible for the comprehensive geriatric assessment and the community health policy of the nursing home. However, their role is limited as the referring general practitioner of each resident is in charge of prescribing their treatment.

The number of physicians who see residents in a facility is small. Only one in 10 of US primary care physicians provides care in a nursing home; 77% of all physicians report spending no time in a nursing home. Only 15% of specialists spend any time in a nursing home. Among physicians who report seeing patients in a nursing home, a majority have spent less than 2 h per week with residents.[23] Contributing to this minimal involvement, over one-third of surveyed physicians report inadequate training in geriatric syndromes such as falls, incontinence, dementia, nutrition and chronic pain.[24]

Medical care in nursing homes focuses on chronic disease and geriatric syndromes, owing to resident comorbid conditions. Functional impairment is the final common pathway of most chronic disease, especially in older persons with multiple advanced disorders.[25] Nursing home residents in the USA are becoming older, increasingly female and more functionally impaired. In these conditions, the challenge is to put the 'home' back in nursing home and not to transform the nursing home into a small hospital.[26]

An estimated 59% of adults with five or more ADL impairments will be admitted to nursing homes.[27] In general, functional status declines with time. Older adults in nursing homes with substantial functional impairment show poorer function at the end of the 6 months than those with higher function[28] and a shorter life expectancy in the nursing home than institutionalized adults of the same age who are less impaired.[29] Functional status is the most sensitive clinical indicator with which to follow disease progression or response to therapy in the elderly. Improvement in function rather than cure of disease is the major therapeutic goal of nursing home care.

Other chronic conditions affect the care of residents in long-term care facilities. Between 45 and 70% of the estimated 1.6 million nursing home residents fall annually.[30] Of these, 30–40% will fall two or more times and 11% will sustain a serious injury as a result of the fall.[31] Urinary incontinence affects approximately half of nursing home residents.[32] Dementia of various types is present in over 60% of typical nursing home residents,[33,34] many of whom exhibit behavioural disturbances.[35] The prevalence of pressure ulcers is higher in long-term care settings.[36] In Medicare-certified nursing home beds, one-quarter of residents receive enteral feeding.[18,37] Weight loss and undernutrition frequently complicate the care of older adults.[38] The prevalence of chronic conditions and interacting comorbid conditions increase the medical complexity of caring for nursing home residents. Several guidelines for the evaluation and management of common clinical problems in the nursing home have been published.[39,40]

Comparison of nursing homes in different countries

In 1997, *Age and Ageing* published a supplement comparing nursing homes in multiple different countries utilizing the data collected by the Resident Assessment Instrument.[41–45] Most of the data were collected in the early 1990s. These findings are summarized in Table 140.1. Some recent data collected using the Resident Assessment Instrument in the USA from 2005 are also included in the table. As can be seen, there is a large variability between countries.

Iceland and Denmark have over 50% of their nursing home population over 85 years of age, whereas in Italy and Japan it is under 40%. Sweden and the USA have over 20% of the nursing home population staying for less than 30 days, whereas none of the Japanese population stay for such a short period. Except in Japan, fewer than one-third of residents are cognitively intact. In the USA, this has changed remarkably in the 10 years since the survey, with now over half of patients being cognitively intact. This almost certainly represents the shift from shorter length of stay in hospitals and more rapid discharge to nursing homes for rehabilitation. Of interest is that in the 1990s, more residents in Japan and Iceland were receiving therapy than were residents in the USA, despite the fact that these two countries had the smallest number of residents staying for less than 30 days.

Table 140.1 Comparisons between nursing homes across countries.

Data collected	Denmark 1992–1993	Italy 1992–1994	Japan 1993	Sweden 1990–1993	Iceland 1994	France 1993	USA 1993	USA 2005
Age								
<65	4.2	4.5	4.6	3.8	1.8	10.2	6.5	–
65–84	45.7	56.1	60.3	52.6	46.6	45.5	53.9	–
85+	50.1	39.3	35.2	43.5	51.5	44.3	47.2	–
Length of stay								
≤ 30 days	2.6	–	0	22.8	0.7	3.8	20.9	–
>2 years	49.4	–	48.5	30.8	60.6	43.8	45.7	–
Cognitively intact	21.8	15.3	32.7	19.7	28.5	11.0	18.5	53.4
Low ADLs	49.0	55.0	42.0	–	38.0	–	48.0	–
Residents receiving rehabilitation	23.0	14.0	30.0	–	31.0	–	11.0	17.2
Restraints	2.2	16.6	4.5	15.2	8.5	17.1	16.5	7.6
Incontinence								
Urine	52.2	54.4	42.9	61.6	56.5	65.2	46.4	55.8
Bowel	22.4	45.3	30.6	39.5	23.0	55.5	29.5	45.8
Participate in activities	52.0	20.0	43.0	–	44.0	–	50.0	–
Nursing time per patient	–	–	84.4	133.7	–	–	118.3	–

There was a low rate of use of physical restraints in Denmark and Japan. The use of physical restraints has halved in the USA in the last decade. In Spain, 39.6% of residents were restrained. As all the evidence shows that restraints do more harm than good, it is extremely puzzling why nursing homes continue to use this form of maltreatment. Of the five countries where social engagement was measured, only Italy had a very low level (20%); in the other countries it varied between 43 and 52%.

In the USA, it is now regulated that all residents have at least some form of social engagement every week.

Nursing time spent with each resident (patient) is highest in England and Wales at 155.5 min and lowest in Japan (84.4 min). In the USA, only 7.5% of the care was given by registered nurses compared with 53.2% in England and Wales. Registered nurses in Japan, Sweden and Spain provided between 14 and 18.2% of the care.

Overall, these studies stress the differences between patient mix and care in different countries. Asian nursing homes in Taiwan showed a moderate level of satisfaction with care, with a monotonous pace of life, inadequate privacy and lost items being the major problems. The average Functional Index Measure (FIM) score was 49.2, which is similar to those seen in the USA in residential care facilities; 74.7% of patients had severe cognitive impairment, physical restraint use was as high as 54%, pressure ulcers varied from 5.3 to 12.1% and the prevalence of stool impaction was 29.4%.[46] As the MDS is more widely used throughout the world, it will become possible to compare nursing homes throughout the world and to develop a gold standard for high-quality nursing homes.

Special nursing home programmes

About half of nursing home residents are diagnosed with dementia.[1] The number of nursing home residents with cognitive dysfunction increased from 39% of long-stay residents in 2004 compared with 25% in 1999.

Dementia is often accompanied by problem behaviours, which can be verbal or physical in nature and can be aggressive or non-aggressive.[47] Good practice in the management of patients with dementia with behavioural symptoms provides an effective alternative to neuroleptics.[48] Special Care (or Needs) Units have been developed in the USA to take care of persons with behavioural problems associated with dementia. These are usually locked units and have a higher staff-to-resident ratio. Many also offer a higher level of recreational therapy. Some of these offer special programmes such as pet or music therapy. Overall, studies have failed to show a major advantage of these units over general nursing home care.

In France, about 44% of the nursing homes have a Special Care Unit. These wards take care of Alzheimer's disease residents with behavioural disturbances, are locked and receive additional funding for organizing non-pharmacological treatment. Innovative strategies such as telemedicine may also be a relevant approach in the nursing home.[49]

Snoezelen is a multisensory therapy that provides easy to-do activities in an enabling environment. It provides a high level of interaction and is both stimulating and relaxing. Although in some nursing homes staff have found it useful, high-quality-controlled studies of its efficacy do not exist. At this time, the small number of available research projects and the small number of participants in each research

Table 140.2 Example of facility quality measure/indicator report.

Facility name_____ **Run date**_____
City/State_____ **Report period**_____
Provider number_____ **Comparison group**_____
Login/Internal ID_____ **Report version number**_____

Measure ID	Domain/ measure description	Facility				Comparison group		
		Num	Denom	Observed percent (%)	Adjusted percent (%)	State average (%)	National average(%)	State percentile
Chronic care measures								
	Accidents							
1.1	Incidence of new fractures	6	198	3.0	–	2.2	2.0	74
1.2	Prevalence of falls	33	215	15.3	–	15.2	13.0	55
	Behaviour/emotional patterns							
2.1	Residents who have become more depressed or anxious	27	215	12.6	–	12.9	16.0	55
2.2	Prevalence of behaviour symptoms affecting others: Overall	34	215	15.8	–	19.5	18.7	42
2.2-HI	Prevalence of behaviour symptoms affecting others: High risk	26	115	22.6	–	23.5	21.8	51
2.2-LO	Prevalence of behaviour symptoms affecting others: Low risk	8	93	8.6	–	8.2	8.0	63
2.3	Prevalence of symptoms of depression without antidepressant therapy	14	215	6.5	–	4.4	5.4	78
	Clinical management							
3.1	Use of 9 or more different medications	105	215	48.8	–	63.1	61.3	14
	Cognitive patterns							
4.1	Incidence of cognitive impairment	1	107	0.9	–	10.9	12.9	23
	Elimination/incontinence							
5.1	Low-risk residents who lost control of their bowels or bladder	49	123	39.8	–	35.7	47.1	64
5.2	Residents who have/had a catheter inserted and left in their bladder	13	215	6.0	5.1	7.6	8.0	39
5.3	Prevalence of occasional or frequent bladder or bowel incontinence without a toileting plan	51	51	100.0	–	27.5	44.5	100[a]
5.4	Prevalence of fiecal impaction	0	215	0.0	–	0.2	0.1	0
	Infection control							
6.1	Residents with a urinary tract infection	13	215	6.0	–	9.6	9.5	33
	Nutrition/eating							
7.1	Residents who lose too much weight	36	208	17.3	–	10.0	10.9	89
7.2	Prevalence of tube feeding	26	215	12.1	–	4.7	7.2	92[a]
7.3	Prevalence of dehydration	1	215	0.5	–	0.6	0.5	74
	Pain management							
8.1	Residents who have moderate to severe pain	15	215	7.0	5.5	8.6	7.8	45
	Physical functioning							
9.1	Residents whose need for help with daily activities has increased	26	193	13.5	–	16.1	18.3	47
9.2	Residents who spend most of their time in bed or in a chair	16	215	7.4	–	3.2	5.5	92[a]
9.3	Residents whose ability to move in and around their room got worse	9	158	5.7	6.2	15.1	17.1	18
9.4	Incidence of decline in ROM	4	214	1.9	–	7.1	8.6	18
	Psychotropic drug use							
10.1	Prevalence of antipsychotic use, in the absence of psychotic or related conditions: Overall	28	188	14.9	–	22.8	21.9	21

ROM, range of motion
Dashes represent a value that could not be computed.
[a]Above or below national average.

Table 140.3 Comparison between quality assurance and continuous quality improvement.

Quality assurance	Continuous quality improvement
Retrospective	Prospective/continuous
Lays blame	No blame
Administrator lead	Team lead
Opinion driven	Data driven
Problem focused	Customer focused
Snapshot	Continuous
Resistant to change	Seeks change

Table 140.4 Problems in the nursing home most amenable to quality improvement.

Depression
Polypharmacy
Pressure ulcers
Undernutrition
Falls
Incontinence
Osteoporosis
Behaviour problems
Lost items
Food quality
Customer satisfaction
Skin tears

Table 140.5 Pharmacy quality assurance report for an academic skilled nursing facility.

	Jan	Feb	Mar	Apr	May	Comparison group[a]
Routine meds(*n*)	9.2	9.4	9.4	9.3	9.7	9.8
PRN meds(*n*)	1.9	1.8	1.6	1.5	1.5	6.5
Antipsychotics(%)	11	7	5	6	4	12.2
Anxiolytics(%)	9	8	11	15	9	22.0
Sedative/ hypnotics(%)	14	7	8	11	9	24.4

[a]Comparison group is to skilled nursing beds in the same city.

Table 140.6 Measurement of quality in a skilled nursing facility utilizing the Functional Index Measure (FIM).

Level of function	Home	Discharge to hospital	Residential care facility
At home prior to event	106	82	106
On admission	77	55	53
At discharge	96	64	69

Table 140.7 The most frequent legal allegations of malpractice against nursing homes.

1 Fall
2 Negligent care
3 Pressure ulcers
4 Lack of care
5 Abuse/assault
6 Dehydration/malnutrition
7 Elopement/wandering

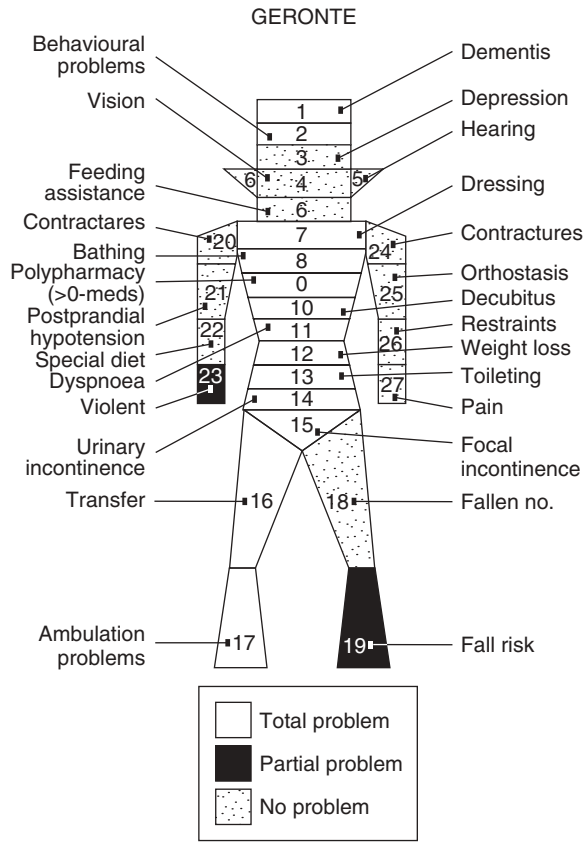

Figure 140.5 A visual communication device: the Geronte, as used by LifeCare Centers of St Louis and the Division of Geriatrics, Saint Louis University.

project prevent a confirmation of this method as a valid therapeutic intervention.[50]

Adapted exercise programmes seem to slow the functional decline[51] and the decline in health-related QOL among institutionalized elderly persons with dementia.

The Eden Alternative involves the introduction of a variety of animals to the nursing home and also the provision of an environment where the residents can be involved in gardening. These environments can improve the home-like

Table 140.8 The IAGG Task Force recommendations.

No.	Recommendation
Recommendation 1	Effective leadership structures are established, that where possible include an expert physician (Medical Director) and an expert registered nurse (Nursing Director) and skilled administrator
Recommendation 2	An international alliance is formed to develop nursing home leadership capacity and capabilities
Recommendation 3	To showcase international exemplars of excellence in nursing home practice to raise awareness of the demonstrable benefits for older people and high standards achieved through expert practice
Recommendation 4	To create positive working conditions for nursing home practitioners with attractive career development opportunities, recognition and similar rewards enjoyed by healthcare workers in comparable roles within the acute care services
Recommendation 5	That nursing home quality indicators are developed that are sensitive to clinical and care needs and the right of older people to care that is dignified and respectful
Recommendation 6	The use of physical and chemical restraints should be reduced to those that are absolutely indispensable
Recommendation 7	That 'meaningful activities' be offered to residents to provide physical and mental exercise and opportunities to participate within the nursing home and in community life, enhancing personal autonomy, social relationships (including intergenerational relationships) and social support
Recommendation 8	That evidence informed pain assessment and management programmes are introduced into all nursing homes
Recommendation 9	That evidence-informed end-of-life and palliative care programmes are introduced into all nursing homes
Recommendation 10	National drug approval agencies consider requiring drug trials that are age appropriate and inclusive of nursing home residents before they are approved
Recommendation 11	IAGG develop international certification courses for nursing (care) home health professionals
Recommendation 12	Pilot the use of 'Community of Practice Models' as a practice improvement method for nursing homes; utilizing both face-to-face interdisciplinary training and virtual team support
Recommendation 13	A universal ethical approach to obtaining informed consent and monitoring the appropriateness of research is developed
Recommendation 14	Develop nursing home research capacity in developing nations
Recommendation 15	An investment is made in research priorities that address major public health problems and inequalities that affect older people receiving long-term care. Research priorities for which a high need is recognized include: a A worldwide survey of different models of care, nursing home structure and issues in improving quality of care is undertaken b A worldwide survey of older persons and their families is undertaken to determine their preferences for long-term care c A cross-national, prospective epidemiological study measuring function and quality of life in nursing homes d Development of culturally appropriate standardized assessment instruments including those involving social participatory methods e A function-focused approach of the prevalence of geriatric syndromes, their impact on function and development of strategies to improve care for these syndromes needs to be developed f Research that evaluates the impact of different models of care against trajectories of physical and cognitive function

quality of the nursing home and encourage visits by young children. Again, however, quality studies demonstration efficacy do not exist.

The measurement of quality of care is fraught with difficulties. Fahey *et al*. compared the quality of medical care for elderly residents in nursing homes with that of elderly people living at home in the Bristol area in the UK.[52] They found that in the nursing home only 74% of those persons with heart disease and 62% of those with diabetes mellitus had had their blood pressure measured within the previous year. In France, 76% of the nursing home women and 60% of men had known hypertension and over 91% of the patients were receiving antihypertensive treatment; 51% of the treated hypertensive patients were well controlled.[53]

In contrast, in the USA, it is the expectation that blood pressure is measured monthly and in persons in Bristol, UK, living at home the rate of measurement was 96%. Only 38% of residents in nursing homes had been prescribed a β-blocker following a myocardial infarction. Nursing home residents were less likely than people living at home to have received a pneumonococcal vaccination, although the rate of nursing home vaccination was similar.

In the USA, studies using the MDS have demonstrated that residents who are incontinent are unlikely to be on a documented scheduled toileting regimen.[54] Troyer found that Medicaid residents had a slightly higher death rate than privately funded residents.[55] Much of this difference was associated with the resident and also the market they were

in. Stevenson found that consumer complaints concerning nursing homes, when made to State Survey agencies, were associated with low nurse aide staffing levels and the number of deficiencies found on the State Survey.[56] Persons who receive potentially inappropriate medications in the nursing home have a much higher chance of subsequent hospitalization or death.[57] Finally, it should be recognized that general practitioners who work in nursing homes will have a higher death rate in their patients than those who work only in the community, making it essential to establish a different standard for these practitioners.[58]

The big picture as given by the recounting above can be reduced to statistics for a single facility so that it can assess its quality and improve its care. Facilities in the USA can use their data as reported in the On-Line Survey Certification and Reporting (OSCAR) and the MDS Quality Indicator data to compare their facility with others in their region, State and the nation (Table 140.2).

The best method to improve care is to put in place a Continuous Quality Improvement plan where data are collected and presented to the interdisciplinary team leaders and staff representatives monthly. When an unacceptable variation in the data is seen, a plan is put in place to determine the reason and to fix the problem. The same data are evaluated each month to allow the team to determine their success at fixing the problem. The differences between continuous quality improvement and old-fashioned quality assurance programmes are delineated in Table 140.3. Areas in the nursing home that are highly amenable to continuous quality improvement programmes are set out in Table 140.4. Examples of monitoring of data in the nursing home for prescribing and efficacy of therapies are given in Tables 140.5 and 140.6. The keys to continuous quality improvement resulting in improved nursing home care are administrative buy-in, team empowerment to fix the problem and continuous collection and feedback of data.

Legal issues in the nursing home

There has been a marked increase in lawsuits against nursing homes in the USA over the last 5 years. In many cases they are frivolous and rely on the fact that the fear of large awards by a jury and the cost of litigation make the nursing home chains settle without going to court. The largest awards are made for elopement (average $860 000) and pressure ulcers (average $293 000). Table 140.7 lists the most frequent allegations against nursing homes.

Visualizing the resident

Communication between all the members of the interdisciplinary team and the physician is often limited. The Geronte is a visual communication device originally developed in France. This single sheet provides a snapshot of the problems that the resident has. Problem areas can be coloured in by any staff member (Figure 140.5).

Improving nursing home care

The International Association of Gerontology and Geriatrics (IAGG) Task Force, in concert with the World Health Organization, has developed a blueprint for improving nursing home care worldwide (Table 140.8).

Key points

- Nursing home facilities are more unique than similar.
- The Minimum Data Set provides a method to compare nursing homes worldwide.
- Nursing homes have short-stay residents who are predominantly there for rehabilitation and long-term residents who require custodial care.
- The introduction of special programmes, for example, the Eden Alternative, increased involvement of physicians and continuous quality improvement methods have improved quality of care in nursing homes.

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CHAPTER 141

Geriatric occupational therapy: achieving quality in daily living

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Overview

Humans are occupational beings

The science underlying the occupational therapy (OT) profession views humans as *occupational beings*.[1,2] Globally, humans are typically identified by their *occupations*. In other words, *who we are* is often determined by *what we do*. What we do are the *activities (occupations)* that comprise our lives. Thus, the focus of OT interventions with and on behalf of older adults is to address their unique needs and preferences for *what they need and want to do in addition to what they are expected to do*, typically concurrently with age-related changes and acute and/or chronic conditions. These p*otential or actual changes in the ability to perform necessary and desired activities (occupations)* impact how elders conduct their everyday lives and present a threat to their overall health and identity.[2–4] Typically, the identity and sense of wellbeing of the elders is expressed through their participation in the activities/occupations that comprise the roles, habits and routines that encompass their lives. These patterns of participation represent who they have been throughout their lives, who they are today and who they may yet become. Participation in society to the extent needed and desired by elders is fundamental to their perception of the quality of personal life and also a basic component of the World Health Organization (WHO) current disability model, the International Classification of Functioning, Disability and Health (ICF).[5]

Conceptual foundations of geriatric occupational therapy

With a simultaneous focus upon intrinsic and extrinsic factors that impact elders' participation in expected, desired and meaningful activities, OT personnel work in partnership with the individual or organizational client to promote the enablement of ageing adults to pursue a meaningful quality of life (QOL) at all levels of care. The WHO conceptual model and OT services interface intimately, as noted in Figure 141.1.

OT interventions centre on enabling elders to pursue the activities, tasks, habits and routines that are personally important and meaningful to them. All of these activities and occupational components contribute to the elders' perception of their QOL. The WHO ICF is the currently accepted model for systematically grouping consequences associated with health conditions. Level of ability, function and/or disablement are seen as a dynamic interaction between the individual's health condition and their personal environmental contextual factors. These intrinsic and extrinsic factors affect the individual's ability to pursue the needed and desired activities that comprise their lives and to participate in individual and group societal functions. If impairment and contextual factors are incompatible, this set of circumstances in turn affects the individual's overall sense of wellbeing and personal perceptions of their QOL.[5]

Person–Environment–Occupation–Performance/Participation model

Figure 141.2 presents the OT Person–Environment–Occupation–Performance/Participation (PEOP) model that is complementary to the WHO ICF model.[6] The PEOP model depicts wellbeing and QOL as a function of the relationship of the personal/intrinsic factors, the environmental/extrinsic factors, occupation/activity and occupational performance/participation in activity and society.[6] These components are shown as being totally interdependent. Figure 141.2 and the following model

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

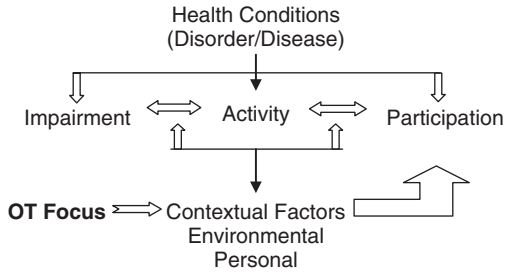

Figure 141.1 WHO ICF model. Adapted from *International Classification of Functioning, Disability and Health (ICF)*, World Health Organization, Geneva, 2001, Figure 1.

express the *P–E–O–P* relationship:

$$\textit{Elder Quality of Life} = f\begin{pmatrix}\textit{Personal Attributes} + \textit{Environmental}\\ \textit{Factors} + \textit{Occupational Performance}\\ + \textit{Participation}\end{pmatrix}$$

where 'elder quality of life' is dependent upon and a function of the *person's* unique health status and functional abilities, plus the degree to which their *environment* supports the *occupations/activities* that they need and want to pursue and allows them to *perform/participate* in society, to meet their requisite needs and desires.

Person (intrinsic factors)

Occupational therapists assess and intervene to enable elders to cope with normal and inherent age-related changes known as *intrinsic factors*. These factors include physiological, motor, cognitive, spiritual, neurobehavioural and psychological components of human function. The older adult's level of motivation, and also roles, habits and routines that comprise their lifestyle, are an integral part of occupational performance and QOL. Hence the capacity for life-long homemakers to continue cooking and taking pride in their culinary creations may be compromised by diminishing olfactory and gustatory ability. In addition, the elders' individual beliefs about themselves and their life experiences – past, current and potential – impact their execution of self-maintenance, work, service, leisure and other activities.

Environment (extrinsic factors)

Extrinsic or environmental/contextual determinants of occupational performance include social support, social and economic systems, culture and values, technology, the built environment and also the natural environment.[6,7] Typically, intrinsic age-related changes in vision, hearing, olfaction, vestibular functions, musculoskeletal and other systems may alter the individual's ability to cope with any or all of these extrinsic environmental factors. The elder's physical surroundings may not adequately support their performance of necessary and desired activities because of age-related changes that they experience. Therefore, in order for elders to continue to live independently (if culturally appropriate) and participate as fully as possible, the inherent changes in sensory and other systems, and also in cognition, may require changes in their physical environment and other external support systems.

Occupation (activity)

What humans do consists of occupation(s). Occupations, better known as *activities*, include all abstract and observable types, and comprise the everyday lives of people of all ages around the world.[8] They also assist individuals in understanding who they are, as humans often define themselves by what they do. When younger adults are asked, 'What do you do?', they may respond by stating their role as student, the type of worker/vocation they pursue or their role as homemaker or parent. When elders are asked the same question, they may respond differently, depending upon what is important to their sense of identity at this later point in life. Nevertheless, occupation/activity in all conceivable forms is the fabric of human existence.

Participation

Active involvement in daily life and various life situations comprises *participation*. This concept includes the ability to perform roles at home, work and in the community. Various factors may hinder an individual's ability to function in one or more of these environments, due to lack of support, attitudes, and physical, social and/or societal barriers.[7,9,10] Throughout their lifespan, individuals encounter different forms of access or barriers to participate in activities that are necessary and meaningful to them.[5,11–14] In the latter years of life, elders may encounter limits to their participation due to decline in age-related or functional abilities, ageism or policies that limit continuation of involvement in activities such as employment or driving.

Scope of occupational therapy services

OT services are provided at three different levels: (1) directly with individuals and/or family/caregiver(s), (2) consultation and administration with community organizations and (3) consultation and/or administration with governmental and/or international agencies. Historically, the majority of services have been provided for individual patients and clients; however, a growing number of community-level OT services have been established during the past several decades. Overall, geriatric OT services are designed to sustain or improve

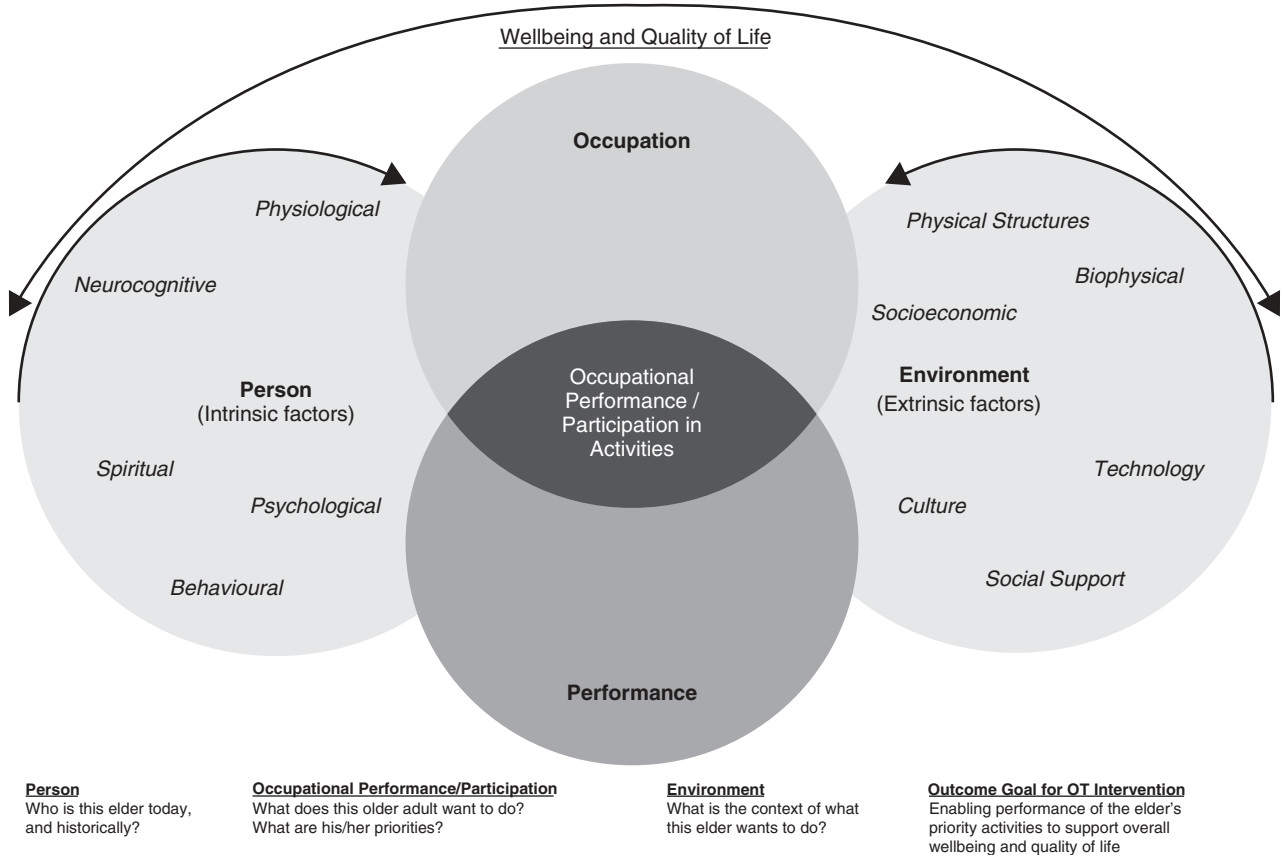

Figure 141.2 Person–Environment–Occupation–Performance/Participation (PEOP) model applied to geriatric OT practice. Adapted from Christiansen *et al*.[6]

the everyday activity-related wellbeing and QOL of older adults. In addition, services aim to enable families, non-governmental organizations and government agencies to mobilize efforts that promote the health of elders, prevent deterioration of function associated with age-related changes, restore functions that are impaired by organic disease, impairment or disability, and/or provide compensatory techniques necessitated by age or disability-related changes. In providing services, OT personnel collaborate with older adults, medical providers and organizations, in order to sustain or improve the ability of elders to perform necessary and meaningful activities, taking into consideration their overall health status, personality, lifestyle, family and/or other support systems. Thus, whether administered with an individual, group or population, OT interventions aim to ensure a QOL commensurate with the elders' priorities, and also those of their family members, carers and their communities.

OT assessment and intervention services are provided collaboratively with or on behalf of older adults who are at risk for or experience limitations due to disease, acute or chronic illness, injury, developmental disability, ageing with an existing disability (e.g. cerebral palsy, spinal cord injury, post-polio) and/or the ongoing ageing process. For example, a person who has sustained a stroke may receive OT services in order to relearn how to dress or to feed themselves. Furthermore, an older adult with dementia may benefit from interventions that simplify tasks and routines, maintain safety within the environment and also support the daily routines and wellbeing of the carer. These services are provided throughout the continuum of care, to address the full range of daily activity (occupation) and participation needs of older clients or patients, as shown in Figure 141.3. The levels and forms of OT services range from the needs of older adults living in the community to the needs of those experiencing end-of-life circumstances.

Hence primary, secondary and/or tertiary settings are included in this continuum of OT services. Primary care OT interventions include provision of health promotion and health protection services within communities, and also for individuals. Examples of these types of services include programmes on home safety to prevent falls and other injuries and driver screening, assessment and retraining, as elders experience age-related changes in function. Secondary care OT interventions include individual, group and/or community approaches for management of health conditions

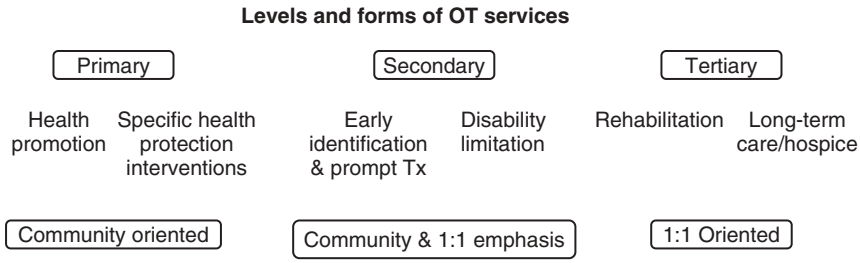

Figure 141.3 Continuum of geriatric OT services.

such as arthritis and Alzheimer's disease. Figure 141.4 displays the categories of services that OTs provide to older adults, their family members, and/or carers.

This topical list depicts typical OT services and is not completely exhaustive. Professional OT services are provided in a range of settings throughout the continuum of care, as shown in Figure 141.5. OT services are coordinated with the providers of healthcare and other services, including physicians, nurses, physical therapists, speech therapists, social workers, community and public health agencies and others, whenever indicated and available. When services are provided on an individual basis, family members and/or other available support systems often become an integral component of the OT service team, to ensure successful intervention outcomes. Furthermore, in addition to working with the older adult, OT personnel provide services to their carers, in order to maximize efficiency, diminish stress and support the health and wellbeing of the carers.

Occupational therapy process

Assessment and intervention

Wherever possible, an evidence-based process is applied to the determination of what should be included in the OT assessment and intervention with elders, as shown in Figure 141.6. In the standard practice in which OT personnel work with an individual older adult, a three-phase process of assessment is followed and considered to be 'best practice'.[15] The first assessment objective is to determine who this individual has been and what does the individual need and want to do, in both a short- and long-term period. The second objective focuses on identifying where and how the relevant current activities, tasks, routines or other occupations can and/or should be done. The third area of concentration in assessment is to determine the biological, psychological and/or social barriers to the elder's achievement of their desired activities. Other individuals or groups may also contribute to the compilation of information on occupational performance issues for the elderly. The Occupational Therapy Practice Framework (OTPF) is the guiding protocol for the OT assessment and intervention process.[6,8]

Occupational profile

The initial step in the OT assessment process determines the client's occupational history and experiences (e.g. summary of activities that have comprised their life to date), and also current patterns of daily living, interests, values

• Transition Planning
  • Meaningful Engagement
  • Employment / re-employment
  • Retirement
  • Loss of spouse/partner
  • End of life
• Development of leisure activities
• Establishing/ re-establishing occupational (activity participation) balance
• Relationships
• Physical activity/ fitness/exercise
• Sexuality
• Spirituality
• Community service
• Use of technology
	• Lifelong learning
	• Assistive product development
	• Home design & accessibility
	• Home management
	• Home safety
	• Shopping
	• Use of alternative/public transportation
	• Driving skills
	• Energy conservation
	• Joint protection
	• ADL
	• IADL
	• Care management
	• End-of-life activities
		Compensatory activity approaches for:
		• Age-related sensory changes including:
		  Presbyopia
		  Presbycusis
		• Tremors
		• Incoordination & balance
		• Weakness
		• Low endurance
		• Arthritis
		• Joint replacements
		• Amputations
		• CVA, TIA
		• Spinal cord injuries
		• Traumatic brain injuries
		• Dementias, including Alzheimer's disease
		• Pain
		• Terminal illness
		• Family/carer/staff skills and coping

Figure 141.4 Geriatric OT services.

Community Based	Institution Based

• Individual homes/apartments
• Senior centres
• Senior housing
• Retirement centres
• Naturally occurring retirement communities (NORCs)
• Elder continuum of care centres
• Learning centres
• Shopping centres
• Parishes, temples, churches and other religious congregations
• Private practices
  • Home modification services
  • Assistive technology/devices interventions
  • Care management
  • Lifestyle redesign programmes
  • Re-employment services
  • Worksite evaluation and remediation
  • Driving skills
• Local, regional, and/or national private or public agencies
	• Acute care
	• Subacute care
	• General medicine services
	• Rehabilitation
	• Adult day services
	• Group homes
	• Assisted living
	• Intermediate care
	• Skilled care
	• Palliative care
	• Hospice care

Figure 141.5 Geriatric OT service settings.

and needs. The client's problems and concerns about performing daily and other relevant life activities are identified, the client's priorities are determined and plans of care and/or management focus on these collaboratively determined priorities.[7] The approach is top-down and client-centred, where enabling participation in personally and culturally relevant and meaningful activities is the focus of planning.[8,16]

Occupational performance assessment

This step in the evaluation process specifically determines the client's biopsychosocial assets, needs, problems or potential problems, based upon results of reliable and valid standardized evaluation instruments. Preferably, the therapist observes the performance of selected activities in order to identify what supports or hinders performance. This skilled observation includes all aspects of the individual's abilities, including affect, cognitive/executive and motor functions. Ideally, the assessment process takes place in the elder's usual environment, typically at home, since performance in an unfamiliar environment may be different. Performance skills, performance patterns, contexts, activity demands and client factors are all considered, but only aspects that are specifically relevant to the desired activities may be assessed. Targeted outcomes are identified, based upon the elder's expressed interests and needs.

The OT assessment of the client's occupational performance takes into consideration all pertinent individual and environmental factors. These factors may include the individual's age, gender, socioeconomic background and current status, racial/ethnic/cultural and/or religious background, developmental status, health history and current status, as well as educational and vocational histories. Interviewing the patient/client and/or the family, whenever feasible, is combined with standardized and other evidence-based performance assessments to determine the individual's profile from which to construct the individualized intervention plan.[17–19] Inquiry covers the following areas:

1 What roles, routines, habits and/or new activities does the patient/client *want to perform (elder priorities)*?

2 What may be done to facilitate the patient/client in the range of activities that they *do perform (current activities)*?

3 What is the patient/client currently *able to perform (intrinsic ability)*?

4 If the individual depends upon a support system, *what activity supports are provided and to what extent*?

5 *Does/do the carer(s) also need OT intervention in order to carry out their support effectively*?

The environment, scope of activities/occupations and roles in which elders typically engage are shown in Figure 141.7. The knowledge of the context, activities and those that comprise the roles that the elder assumes assists OT personnel in collaborative assessment and intervention with elderly clients, their carers, families and other support systems.

Where multiple environmental factors serve as barriers to participation in necessary and desired activities and thereby impact the wellbeing of older adults, OT practitioners collaborate with other disciplines in evaluating the individual's circumstances and planning appropriate interprofessional interventions. On an independent basis, OT personnel frequently evaluate facilities or the elder's home, in order to facilitate PEOP compatibility. The evaluations compare the elder's activity needs and priorities with their functional abilities and the physical environment in which they function, in order to determine and predict the likelihood of their success in being able to perform these activities. The identified deficiencies are then targeted in the intervention plan.

OT is concerned with how elders perform in their daily lives and how performance affects their engagement in occupations (activities). These occupations typically are components of performance that support their participation in the habits, routines and roles that provide meaning to their lives. Thus, the evaluation process determines what the patient/client needs and wants to do, what are their functional capabilities, and what are the barriers or supports needed to perform those priority occupations.[8]

When interventions are indicated, due to a poor PEOP fit, OT personnel work with the elder and family or other support systems to improve these factors. Recommendations may include specific changes to the physical environment, compensatory changes in their routines and activities and/or assistive equipment to permit successful

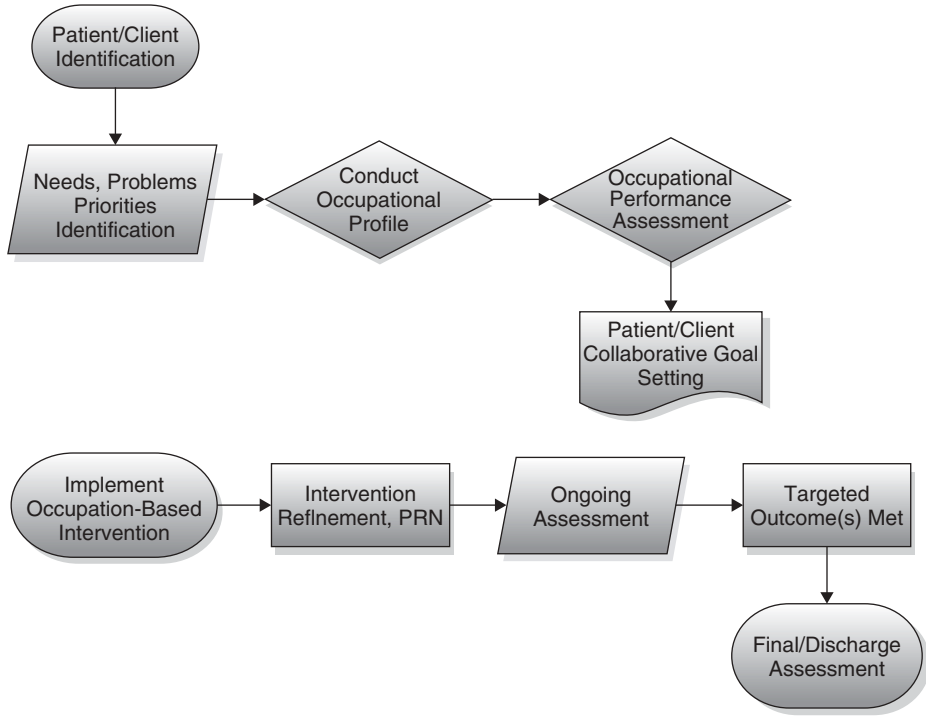

Figure 141.6 OT process.

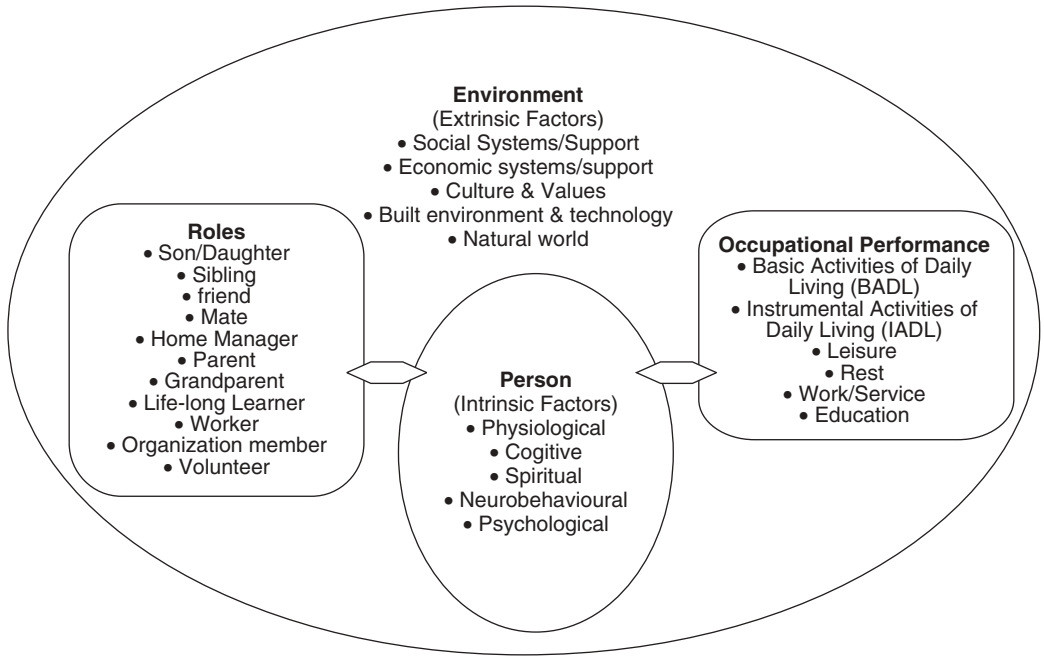

Figure 141.7 OT assessment and intervention components.

occupational performance. These needs are often overlooked completely or underestimated when the individual is being discharged from one level of medical care to another or to their home. When this insight is lacking, the gaps in environmental support may put the older adult at increased risk for dependency, in addition to falls and other injuries.

Intervention

Development of the intervention plan

OT personnel individually tailor the interventions to the patient/client's needs in order to promote optimal outcomes. The intervention plan is thus developed collaboratively with the client and their family, if indicated, so that appropriate strategies, specific interventions and targeted outcomes are included and mutually agreed upon. Therefore, the approach utilized to increase functional level in ADLs, IADLs and also self-esteem, socialization and a sense of personal competence in whatever is pursued is unique to each patient/client.

Intervention implementation via client-centred care

Utilizing goal-directed activities that are meaningful to the patient/client, depending upon the nature of their health status, the OT assists the individual to adapt temporarily or permanently to the physical and social environment that circumscribes their life. This approach promotes mastery of essential living skills, and also those skills that represent the patient/client's other priority interests. As a group, elders exemplify highly diverse lifestyles and interests. Therefore, OT personnel identify modalities and activities that are motivating to the patient because they are relevant to their particular lifestyle. Collaboration with the patient/client, known as *client-centred care*, facilitates and enables the mobilization of the individual's internal psychological resources. This process then promotes greater participation in the intervention, which in turn optimally assists in restoring or enhancing function where functional change or decline has occurred or is threatened. If indicated, family members or other carers are included in planning and implementation, depending upon the needs of all relevant members. All interventions are continually documented, monitored, re-evaluated and adapted or discontinued, based upon the client's overall status.

OT interventions may include any or all of the following categories.

Use of occupation to enhance quality of life

Health promotion

Most individuals' lives are comprised of a variety of self-maintenance, productive, leisure and/or service activities. Thus OT personnel utilize occupations (activities), tasks, roles, routines and/or habits as therapeutic agents in achieving long-term and short-term goals toward adaptation and habilitation, restoration of function and/or enhancing the individual's QOL. Many health promotion programmes are provided in the community; however, OT personnel integrate health promotion perspectives in services throughout the continuum of care[4,8,20,21] (see Figures 141.3–141.5).

End of life

The latter applies also to OT's promotion of QOL and independence in daily occupations with terminally ill patients, to the extent possible for as long as possible. OT also facilitates maintenance of ADLs, pain management, joy, life review and other meaningful closure activities at the end of life by assisting the elder and their family members to participate in meaningful activities with terminally ill individuals.

Community-level instruction and patient/client education

In community settings, OT personnel provide health promotion and other training programmes for the elders, family members, carers and agency employees.[20,21] The content is tailored to the needs of the target group, just as when interventions are implemented for individuals. Subjects covered include those identified or related to those given in Figure 141.4.

In acute or subacute care, rehabilitation and home healthcare, collaborating with the older patient/client in basic skills training or retraining in functional occupations (e.g. ADLs and/or IADLs) are standard components of OT practice. Interventions may also focus on making positive transitions in overall lifestyle based on physical, emotional, and/or retirement, continuing employment and service needs of elders.[1,2] Furthermore, the OT personnel collaborate, wherever indicated, with other healthcare providers in the rehabilitation team as well as community agencies to promote optimal patient/client outcomes.[8,22,23]

Since older adults and their support systems may not be aware of age-related physiological and psychological changes, OT may also employ education or training in these areas to facilitate adaptation to deterioration of function and adjustments in relationships. Topics may include the use of compensatory strategies, recommendations for equipment and other methods to compensate for loss of function and ensure the ability to participate in meaningful occupations. Health promotion teaching strategies may include the following: [20]

- Prevention of physical deterioration through the use of age-appropriate approaches for participation in activities:
  - body mechanics
  - joint protection
  - energy conservation
  - activity and exercise guidelines

• Prevention of psychosocial deterioration through the use of occupation:
  – adjustment of lifestyles to accommodate age-related, role and other changes in life
  – the role of purposeful, balanced activities in maintaining health and overall wellbeing
  – overall time management
  – self-esteem, empowerment, mastery strategies
  – interpersonal skills and socialization activities
  – an emphasis on positive aspects of living in promoting a healthy lifestyle

Remediation strategies for functional decline

OT interventions to compensate for sensorimotor occupational performance deficits focus on enabling the elder to participate in the activities identified for maintenance of function and/or improvement of function. These activities include sitting and standing balance, strengthening, endurance, range of motion and coordination. Therapeutic approaches employed in all of these occupational performance skills areas are related in the intervention process to ADL and IADL participation, including related tasks and roles performed by and meaningful to the individual.

Furthermore, comorbidities that the older adult experiences are simultaneously factored into the intervention approaches. Interventions are individualized to accommodate cognitive, behavioural and affective changes that occur following a stroke and/or other neurological conditions, as in dementias or Parkinson's disease. When oral–motor dysfunction, muscular rigidity, joint pain, bradykinesia or other symptoms impede direct intervention, OT practitioners utilize facilitatory techniques and positioning approaches. These interventions focus on enabling the elder to participate in functional, meaningful activities that accomplish the desired mobilization and overall rehabilitation goals. OT personnel also develop therapeutic programs in a wide variety of settings, which are shown in Figure 141.5.

Physical environment adaptations

Because of normal age-related changes, OT consultation and implementation of specific environmental adaptations and modifications may be indicated for most elders, in order to facilitate their continued participation in the activities that are important to them. Where individual or comorbid conditions limit participation, personally relevant physical environmental modifications may be recommended. Additional lighting, railings, ramps, grab bars and assistive devices may be indicated, in order to promote accessibility and independence in mobility and the ability to pursue the elder's necessary and desired occupations. OT interventions also include methods to compensate for cognitive, memory and psychological changes. These compensatory accommodations that can be implemented in existing or new facilities may make the difference between the elders' dependence and their meaningful participation. OT personnel also provide suggestions for environmental adaptations relative to therapeutic programming and activities for persons with dementia, including cognitive integration, orientation, memory, safety and pursuit of meaningful activities.

Technological aids and devices

Both low and high technological assistive devices may be recommended to enhance the elder's occupational performance and participation in solitary, group or community activities. Low vision aids and assistive devices for hearing loss are examples of equipment that may be recommended for use if sensory deficits result in occupational performance deficits. OT personnel often recommend assistive devices for individuals who demonstrate limitations in sensorimotor function, range of motion, strength, coordination and endurance. Different types of assistive devices may be suggested for persons who demonstrate occupational performance deficits in their cognitive abilities. Overall, devices are recommended only if they support improved participation in the activities that are important to the elder and/or their family or other support system.

Intervention review

As noted earlier and depicted in Figure 141.6, OT interventions are continually reviewed and refined, as indicated. Periodic reassessment of the client's status, including ongoing inputs from the elder and/or their carers, family members and other support systems are integrated into any alterations in the intervention plan. When the targeted outcomes are met, or it is determined that the elder may not be able to achieve the outcomes despite refinement of the intervention plan, the elder undergoes a final assessment process and is discharged or discontinued from OT services.

Outcomes (engagement in activity to support participation)

Outcome assessment information determines the extent to which the targeted goals and objectives of the intervention were met. This information is used to plan future collaborative therapy with the client, discontinue services, and evaluate the service programme.

Case examples

Case 1

An 86-year-old Caucasian woman, Irene, was admitted to a local acute-care hospital following a right hip fracture sustained when she fell from a chair while trying to change a light bulb. She was scheduled for a hip replacement.

OT intervention

During her hospitalization, OT personnel met Irene and completed an occupational profile that informed the therapist about this elderly woman – in particular, her

lifestyle and the activities that she needed and wanted to do. She was provided with a long-handled reaching device to enable her to more easily reach items in her hospital room and at home, once she was discharged. The OT learned that Irene enjoyed knitting and recommended that her daughter bring her mother's current knitting project to the hospital during her stay. Knowing that her right hip mobility would likely be limited for the weeks during her recovery from the hip replacement surgery, the OT worked with Irene on donning her socks, using a sock-aid, and continually reinforcing postsurgical hip precautions. During her hospital stay and immediately prior to discharge, the OT reviewed all ADL and IADL implications, and also other high-priority activities that Irene identified during her initial occupational profile. Irene agreed to have the OT arrange for her to have an elevated toilet seat with attached rails, a tall shower stool, a handheld shower and grab bars for her home shower for her use following discharge from the hospital. Additional recommendations were made regarding the height of the furniture that Irene would use at home for sitting, eating and knitting. Irene's daughter agreed to obtain extensions for the legs of Irene's favourite easy chair, so that she would be able to sit and rise from the chair easily. At the time of discharge, Irene's daughter stated that she felt that her mother was well prepared to manage at home during the remainder of her recovery and, most important, Irene agreed.

Case 2

A 65-year-old African man, Kwesi, who completed initial acute care and rehabilitation treatment for a cerebral vascular accident (CVA) with left-side hemiparesis and mild expressive aphasia, was referred for continued OT upon discharge to his home.

OT intervention

His wife and the OT collaborated with Kwesi in determining the priorities of his current activities and target goals. At this point, he was dependent upon his wife for assistance with toileting, bathing and dressing and was not performing IADL tasks that he had assumed prior to his CVA. These activities, plus rejoining his men's group, were very important to him. Therefore, over the next several weeks, his OT worked with him to upgrade his independence. Since organizing and sequencing the steps within those activities were still difficult, the OT provided him and his wife with strategies to enable him to relearn the steps that were problematic. These included transfer assistance to the toilet and into the bathtub with the use of a bath bench, organizing clothes within easy reach and by colour groups to identify appropriate combinations easily, and relearning his use of the telephone. The OT also worked with his wife to help her realize more success and improved coping with her husband's condition, in addition to having more time for the activities that were important to her. Throughout this process, the OT coordinated the intervention plan with Kwesi's physician and other healthcare providers.

Case 3

A 75-year-old immigrant from Bosnia, Soofi, was found wandering several miles from her neighbourhood. Her family, with whom she lived, was referred to neurological/psychiatry services for her to receive a complete work-up for probable dementia.

OT intervention

Following her evaluation by a neurologist, Soofi was referred to OT for assessment and intervention. The occupational therapist therefore scheduled a time to meet with Soofi and her family at their home, in order to obtain the most accurate information regarding her occupational performance within her usual environment. In addition, the OT would observe and discuss the nature of the support that Soofi needed and that the family provided for her. This would also provide an opportunity for the OT to adapt approaches to address cultural needs, if indicated. Results of the assessment process indicated that Soofi had difficulty with sequencing her hygiene maintenance and dressing and she also typically awakened in the early hours of the morning, rummaging through her room and the kitchen trying to find items and creating enough noise to awaken the household. The OT worked with the family over several sessions in the home to assist them in simplifying the organization of Soofi's room and the kitchen. Part of the approach involved mounting pictures of the types of clothing in her dresser on the drawers and also on the outside of the kitchen cabinets, so she could better associate the items she was seeking in the relevant location. Furthermore, the OT worked with the family to adjust Soofi's routine to facilitate a more predictable schedule. The family was also informed of the supportive resources provided by the local Alzheimer's Association.

Conclusion

OT focuses on the elder's ability to participate in the activities that comprise their lives and that are important to them. The aims of interventions are to (1) collaborate with the older adult to plan client-centred care, (2) tailor the approaches to meet the elderly patient's/client's activity needs and (3) address the elder's continued participation in society in a manner that is appropriate and meaningful to that individual, thus affecting their overall wellbeing and quality of life. Fundamental concerns of OT practitioners include supporting the elder's autonomy in setting priorities and making decisions regarding their participation and maintaining a level of mastery and control over their environment and lifestyle. OT personnel foster an enabling therapeutic relationship with older adults of all ability

levels throughout the continuum of care, together with their families and/or other support systems. The emphasis of OT on the elder's ability to participate in meaningful occupations promotes cost-effective care, individual competence and optimal quality of life.[1,2]

Key points

- Humans throughout their lives are *occupational beings*. Thus, *who we are* is typically framed by *what we do*. OT is patient/client centred, collaborative and focuses on what the individual *needs* and *wants to do*.
- OT services aim to sustain or improve the elders' ability to perform necessary and meaningful activities (*occupations*), whether they are long term and historically a part of the elder's life, newly acquired interests and roles or future desired activity goals.
- OT identifies the strengths and priorities of the patient/client and partners with the individual and their family members or other support systems to ensure their participation in the occupations that sustain their overall health and quality of life.
- OT interventions focus on supporting age-related changes and/or comorbidities that affect the elder's ability to participate in desired activities/occupations. Interventions thus target the individual's biopsychosocial occupational performance abilities and often include adaptive approaches and assistive devices that compensate for any existing occupational performance deficits.
- OT services are provided throughout the continuum of care, from primary care health promotion and wellness approaches to interventions in tertiary, long-term care, palliative and hospice settings.

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CHAPTER 142

Geriatric medicine education in Europe and the United States

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Introduction

During the twentieth century there was a remarkable increase of >30 years in life expectancy in developed countries.[1] It has been recently estimated that the majority of babies born since 2000 in these countries will reach 100 years of age if the current gain in life expectancy continues during the twenty-first century.[1] As a consequence of this fast process of ageing of the population, a new category of patients has appeared, characterized not only by advanced age but also by the simultaneous occurrence of multimorbidity, disability and frailty.[2] A cross-sectional analysis conducted on a random sample of more than one million Medicare beneficiaries aged 65 and older living in the United States in 1999 revealed that 65% had multiple chronic conditions.[3] Older patients with multimorbidity tend to have more rapid declines in health status and a greater likelihood of disability.[4,5] A recent Italian study of older patients cared in acute care wards, home care and nursing homes in Italy confirmed that the majority of these patients are aged >80 years, suffer from multiple diseases and have severe disability in ADL.[6]

Unfortunately, there is still a huge gap between the healthcare needs of these patients and the ability of the healthcare system to satisfy them. Part of the responsibility of the current healthcare crisis lies in the medical education, which has traditionally focused on single diseases, and particularly on acute conditions requiring hospital care, and therefore is more and more inadequate in preparing physicians for their future practice, which will often consist of providing effective healthcare for patients suffering from multiple chronic diseases, i.e. mainly the older patients.[7]

The failure of medical education to adequately prepare physicians for the care of older patients has been acknowledged for the last 20 years,[8] but the situation has not significantly improved, except for the slow and heterogeneous diffusion of geriatric medicine in undergraduate and postgraduate medical curricula.

In this chapter an overview of current geriatric education in Europe and United States will be provided.

Geriatric education in Europe

The Council of Europe includes 45 state members, while the European Community, limited until May 2004 to 15 countries, includes nowadays 27 different countries, with varying degrees of industrialization, economic benefits and employment. These initial remarks highlight that it is not possible to consider Europe as a homogeneous group of countries. The wide variation of demographic data is probably the best way of showing the 2008 disparity among the European countries:[9]

- Birth rate: the highest is in Iceland (2.2/woman) and the lowest in Slovakia (1.3/woman);
- Mortality rate during the first year of life: the highest is in Turkey (16.0/1000) and the lowest in Luxembourg (1.8/1000);
- Life expectancy at birth for men: the highest is in Liechtenstein (79.9 years) and the lowest in Lithuania (66.3 years);
- Life expectancy at birth for women: the highest is in Switzerland (84.6 years) and the lowest in the former Yugoslav Republic (76.5 years).

However, in more developed European countries, life expectancy at birth continues to increase: there is actually a 3-month 'bonus' of life for each year of life.[10] In 2008, the European Union (EU) (27 countries) had a total population of 501 million inhabitants, of which 17% were over 65 years. Between 2010 and 2050, the EU (27 countries) dependency rate (ratio between people over the age of 65 and people

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between the ages of 15 to 64.9) is expected to increase from 25.9 to 59.4.

The number of nonagenarians, centenarians and supercentenarians (over 110 years) will continue to increase.[11] While the healthy life expectancy is longer than ever in developed countries, still many older subjects spend the last years of their life suffering from chronic diseases and increasing disability, which explains why a large percentage of patients requiring healthcare belong to this age-group.

In this context, the promotion of training in geriatric medicine should be a priority in every European medical schools with the following aims: (1) to improve the understanding and integration of the ageing process within the life cycle, (2) to increase the basic and more specialized knowledge of chronic and disabling diseases, (3) to perform comprehensive assessment of the ageing and aged old persons in order to guarantee a better follow-up of the patient, and (4) to guarantee more suitable care, including the appropriate use of drugs in older subjects, neglecting neither ethical nor costs of care issues.[12,13]

In the 1990s, a first European geriatric education survey was performed by a small group of professors of medical gerontology whose three goals were: (1) to establish the basis of a consensual undergraduate core curriculum, (2) to be politically active in order to obtain the creation of a chair of geriatric medicine in each European medical school, and (3) to set up a long-life training course to teach and train the future academics in geriatric medicine.[14] Fifteen years later, an update was realized to evaluate the degree of achievement of these goals, the real situation at the beginning of a new millennium and the needs of professional academic specialists to better cope with the increasing care demand of the future older subjects.[15] In this chapter a further update of the data of these two surveys will be provided.

Among the 31 European countries included in the 2008 survey, Geriatrics is:

– a medical speciality in 16 countries (Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Lithuania, Macedonia, Malta, the Netherlands, Spain, Sweden and United Kingdom);
– a medical subspeciality in 9 other countries (Iceland, Ireland, Norway, Poland, Serbia and Montenegro, Slovakia, Switzerland, Turkey and Ukraine);
– not recognized as a specialty in 6 countries (Austria, Estonia, Greece, Luxembourg, Moldavia and Slovenia).

It is interesting to point out that the existence of geriatric nurses is recognized only in 13 European countries (mainly those in which geriatrics is considered as a medical speciality). However, recognition of the existence of a specialty does not imply that gerontology and geriatrics are included in the medical education curricula.

In seven European countries a chair of Geriatrics exists in all medical schools; the chair is most often filled but in a few cases the chairperson has not been nominated yet or is in the process of being appointed (Belgium, Finland, France, Iceland, Norway and Sweden). In several European countries, a chair of Geriatrics exists in some medical schools (80% Switzerland, 70% in Italy, 50% in the Netherlands and Serbia, 33% in Denmark and Austria, 36% in Spain and only 16% in Germany and Portugal). Moreover, no chair of Geriatric Medicine exists in Estonia, Greece, Luxembourg, Malta, Macedonia, Moldavia and Slovenia. It is interesting to notice that two countries (Macedonia and Malta) do not have a geriatric chair even if Geriatrics is recognized as a medical speciality.

Undergraduate geriatric medicine education in Europe

Although the European Union of Medical Specialists – Geriatric Medicine Section (GMS-UEMS) has produced an undergraduate curriculum in geriatric medicine in 2003, which has been approved by a number of national geriatric societies, there is no evidence that this curriculum has been implemented in the majority of EU countries.[16]

Undergraduate teaching of geriatric medicine is organized in 25 countries, but it is mandatory in only 9, and nonexistent in 6 of the 31 surveyed European countries. The existing teaching activities are based on European/National core curriculum in only 2 countries, while in general, the content is independently determined by each medical school. Thus, variability is high both in teaching hours and curriculum. The mean number of teaching hours devoted to geriatrics varies considerably from one to another country, with a maximum of 100 hours in Norway, 60 hours in Serbia and Spain, 50 hours in Italy, Slovenia and Slovakia, 40 hours in Finland and Iceland, 30 hours in France, Hungary and Poland, 20 hours in Denmark and Germany, between 10 to 15 hours in Belgium, Czech Republic, Lithuania, Malta and Turkey and less than 10 hours in Ireland and Luxembourg. Within each country variability is also high. In 10 of these countries, geriatric teaching takes place at different times of the medical studies. Again, the differences are wide from one country to the other, but in most cases, geriatric teaching takes place in the second half of the medical studies, i.e. between the 4th and the 6th year. Moreover it is important to notice that the teaching methodology is 'problem-based learning' in nearly 50% of cases. Undergraduate teaching activities are organized in all medical schools of only 14 countries of the 31 surveyed, while clerkships are available in 16 of these countries (11 mandatory and 5 elective).

Geriatric medicine teaching at the postgraduate level

Postgraduate teaching activities are specifically organized by geriatricians in 16 European countries (Belgium, Czech Republic, Finland, France, Hungary, Ireland, Italy, Lithuania, Malta, the Netherlands, Norway, Poland,

Slovak Republic, Spain, Sweden and United Kingdom) and in collaboration with internal medicine in 6 other countries (Germany, Iceland, Serbia, Switzerland, Turkey and Ukraine). Geriatric postgraduate teaching does not exist in 9 countries. In countries organizing postgraduate teaching activities, students are selected on a pre-requisite basis (N = 9) and the course is based on a pre-established core curriculum (N = 16). A final mandatory examination takes place at the end of the course in 13 countries and a mandatory re-validation is needed in only 8 countries.

Continuing medical education

Continuing medical education (CME) in geriatrics is organized in 18 different European countries, but is mandatory in only 11 of them (Austria, Belgium, Czech Republic, Finland, Hungary, Italy, the Netherlands, Poland, Slovakia, Switzerland and Ukraine).

Undergraduate geriatric education in the United States

Even as the post-World War II 'baby boom' generation ages and requires more medical care, the United States (USA) is facing a critical shortage of geriatricians. In the USA, there have been ongoing efforts to increase medical students' early exposure to geriatrics in the hope of increasing the number of students selecting a career in geriatric medicine. However, to ensure that ageing Americans have access to adequate medical care, for over 20 years the American Association of Medical Colleges (AAMC) has recommended that all physicians should be educated and trained to treat geriatric patients, even if not as a specific specialty focus.[17,18]

Even though only 10% of all US medical schools had a required geriatric medicine clinical rotation in 2001, 92% of medical schools included geriatrics education within some required course. By 2005, this proportion grew to 98%.[19] Additionally, a growing number of US medical schools are reporting having identifiable geriatrics curricula. Most schools have sections or divisions of geriatrics or gerontology in departments of internal medicine or family practice. However, few medical schools in the USA have a dedicated department of geriatrics.[19] Ongoing foundational and government-supported programmes such as the John A. Hartford Foundation or the Donald W. Reynolds Foundation also aim to increase exposure to geriatrics in medical school in the USA.

Postgraduate geriatric education in USA

Residency

Primary care Graduate Medical Education (GME) in the USA has traditionally had a paucity of specific training in the comprehensive management of geriatric patients. Nearly two-thirds of America's internists report being undertrained in chronic care management as a result. In 1993, the Institute of Medicine (IOM) recommended that primary care residency programmes should include at least nine months of geriatric training.[17] As a result, internal medicine residency programmes have increased their geriatric training, with over 90% of programmes requiring dedicated geriatric training of at least two weeks' duration. Despite this, only a minority of internal medicine residencies require six or more weeks of geriatrics training, which mostly exist in the form of block rotations. More than 95% of family medicine residency programmes now have a required curriculum, not just a curricular component, in geriatrics. However, only one quarter of family medicine residencies require four or more weeks of geriatric medicine training during their residency.[20]

Fellowship

According to the IOM report, there are approximately 7100 geriatricians, and the numbers are declining – even as the US population rapidly ages. Because the number of geriatricians has grown slowly over time and nowhere near the rate of the ageing population, in 1998 the American Boards of Internal Medicine and Family Practice reduced from two years to one the duration of the fellowship required for eligibility to sit for the qualifying examination for the Certificate of Added Qualification (CAQ) in Geriatric Medicine. This reduction resulted in the elimination of educational methods, research and leadership from the training of most geriatrics.[21] Despite this, the rate of unmatched geriatric fellowship positions has been rising, in part due to the relatively poor reimbursement rates for geriatricians in practice compared to procedure-based specialties and the increased burden of student loans for graduating students in the USA. Discussions at the national level to promote entry into primary care specialties, and subsequently the field of geriatric medicine, are underway and include loan repayment programmes as well as enhanced reimbursement systems for geriatric care.[20] The recruitment of high-quality US medical school graduates into geriatric medicine continues to be a challenge.

Initiatives for improving undergraduate and postgraduate geriatric education: United States

The Donald W. Reynolds Foundation has undertaken a major effort to strengthen the training in geriatrics of medical students, residents, practicing physicians and affiliated healthcare professionals. During the past decade, the Foundation has provided support to 2 departments of geriatrics, 30 medical schools to improve medical education

Table 142.1 Minimum geriatric competencies for medical students (USA).[18]

Medication Management

1. Explain impact of age-related changes on drug selection and dose based on knowledge of age-related changes in renal and hepatic function, body composition and central nervous system sensitivity.
2. Identify medications, including anticholinergic, psychoactive, anticoagulant, analgesic, hypoglycaemic, and cardiovascular drugs, that should be avoided or used with caution in older adults, and explain the potential problems associated with each.
3. Document a patient's complete medication list, including prescribed, herbal, and over-the-counter medications, and, for each medication, provide the dose, frequency, indication, benefit, side effects, and an assessment of adherence.

Cognitive and Behavioural Disorders

4. Define and distinguish among the clinical presentations of delirium, dementia and depression.
5. Formulate a differential diagnosis and implement initial evaluation in a patient who exhibits dementia, delirium, or depression.
6. In an older patient with delirium, urgently initiate a diagnostic workup to determine the root cause (aetiology).
7. Perform and interpret a cognitive assessment in older patients for whom there are concerns regarding memory or function.
8. Develop an evaluation and non-pharmacological management plan for agitated demented or delirious patients.

Self-care Capacity

9. Assess and describe baseline and current functional abilities (instrumental activities of daily living, activities of daily living, and special senses) in an older patient by collecting historical data from multiple sources and performing a confirmatory physical examination.
10. Develop a preliminary management plan for patients presenting with functional deficits, including adaptive interventions and involvement of interdisciplinary team members from appropriate disciplines, such as social work, nursing, rehabilitation, nutrition and pharmacy.
11. Identify and assess safety risks in the home environment, and make recommendations to mitigate these.

Falls, Balance, Gait Disorders

12. Ask all patients over 65 years old, or their caregivers, about falls in the last year, watch the patient rise from a chair and walk (or transfer), and then record and interpret the findings.
13. In a patient who has fallen, construct a differential diagnosis and evaluation plan that addresses the multiple aetiologies identified by history, physical examination and functional assessment.

Health Care Planning and Promotion

14. Define and differentiate among types of code status, healthcare proxies, and advance directives in the state where one is training.
15. Accurately identify clinical situations where life expectancy, functional status, patient preference, or goals of care should override standard recommendations for screening tests in older adults.
16. Accurately identify clinical situations where life expectancy, functional status, patient preference, or goals of care should override standard recommendations for treatment in older adults.

Atypical Presentation of Disease

17. Identify at least three physiological changes of ageing for each organ system and their impact on the patient, including their contribution to homeostenosis (the age-related narrowing of homeostatic reserve mechanisms).
18. Generate a differential diagnosis based on recognition of the unique presentations of common conditions in older adults, including acute coronary syndrome, dehydration, urinary tract infection, acute abdomen and pneumonia.

Palliative Care

19. Assess and provide initial management of pain and key non-pain symptoms based on patient's goals of care.
20. Identify the psychological, social and spiritual needs of patients with advanced illness and their family members, and link these identified needs with the appropriate interdisciplinary team members.
21. Present palliative care (including hospice) as a positive, active treatment option for a patient with advanced disease.

Hospital Care for Elders

22. Identify potential hazards of hospitalization for all older adult patients (including immobility, delirium, medication side effects, malnutrition, pressure ulcers, procedures, peri- and postoperative periods, and hospital acquired infections) and identify potential prevention strategies.
23. Explain the risks, indications, alternatives, and contraindications for indwelling (Foley) catheter use in the older adult patient.
24. Explain the risks, indications, alternatives, and contraindications for physical and pharmacological restraint use.
25. Communicate the key components of a safe discharge plan (e.g., accurate medication list, plan for follow-up), including comparing/contrasting potential sites for discharge.
26. Conduct a surveillance examination of areas of the skin at high risk for pressure ulcers, and describe existing ulcers.

at their institutions, and 4 consortium schools aimed at developing faculty to teach geriatrics. Overall, it appears this funding strategy was has been successful in achieving its goals of enhancing geriatrics education. The investment of the Reynolds Foundation in the development of geriatrics curricula, programmatic development and training at US medical schools continues to influence undergraduate, graduate and practising physician education.[22]

The John A. Hartford Foundation has had a longstanding commitment to geriatrics education at all levels of learners including the surgical and related specialties. With the AAMC, the Hartford Foundation has advanced geriatric and gerontology studies through integrative and innovative curricula. Forty of the 126 eligible medical schools received a total of $100 000 each for two years to create and implement a four-year undergraduate curriculum incorporating geriatrics education.

The Health Resources and Services Administration (HRSA), an agency of the US Department of Health and Human Services, is the primary federal agency for improving access to healthcare services for people who are uninsured, isolated or medically vulnerable, including elders. Through Geriatric Education Centers (GEC), as well as the establishment of Geriatric Academic Career Awards (GACA), HRSA has helped educate, train and retain health professional faculty, students and practitioners in the diagnosis, treatment and prevention of disease, disability and other health problems of the aged.

At the 2007 Geriatrics Consensus Conference, hosted by the AAMC, more than 450 experts in geriatric medicine including medical professionals, educators, experts and leaders devised a set of 26 competencies in 8 domain areas for evaluating the quality of the geriatric curriculum and its benefits, entitled 'Geriatric Competencies for Graduating Medical Students' (see Table 142.1). This effort has been a major first step in setting the standard of care of elders for US healthcare providers.[18]

Conclusion

In Europe as well as in the USA undergraduate and postgraduate training programmes in geriatrics are varied in content and format and in general are inadequate to provide physicians with the knowledge and skills that are necessary to provide effective healthcare to older patients. Restructuring the educational process taking into account the healthcare needs of the ageing societies can no longer be deferred. Otherwise, there is a risk of a progressive collapse of European and American healthcare systems under the burden of the multimorbidity and disability of the rapidly increasing older population.

Key points

- Ageing of the population has been very fast in Europe and the United States during the last century and it will continue in the next decades. Whereas the majority of older people live healthy and independent lives, the risk of morbidity, ill health and disability increases with age.
- The frail elderly population with its specific medical and psychosocial needs requires high-quality geriatric care: this can be provided only if appropriate geriatric training is guaranteed to all categories of healthcare professionals and, particularly, doctors.
- In many European countries and in the USA, undergraduate training in gerontology and geriatrics is not adequately developed and is not integrated into the medical curricula, particularly with basic and preclinical disciplines.
- Postgraduate training in geriatric medicine is available in the USA and in some European countries, but not in others. In general, the number of geriatricians is still inadequate to match the increasing number of older patients with multimorbidity and disability requiring healthcare.

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CHAPTER 143

Systems of healthcare: the United States

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Introduction

The extraordinary growth in life expectancy at birth in nearly all countries of the world reflects an ongoing revolution in longevity. This revolution has resulted in both survival of individuals to older ages and a changing age distribution of the entire population. The impact of the longevity revolution has been pervasive and profound. The impact is felt financially, socially and politically throughout the United States (USA). This trend has resulted in significant healthcare changes, both on an individual and societal level.

Developed nations across the world have approached the ageing population and need for expanded health services in a variety of ways. Home health, hospital-based and nursing home care have experienced a profound increase in complexity over the last quarter century. This complexity of care is reflected in the expansion of funding arrangements, number of service providers, and geographic service areas. Governmental expenditures for healthcare services have continued to rise but are not sustainable at the current rate. The development and passage of the Health Care Reform Bill has attempted to slow the rise in spending while promoting increased quality and universal access to care healthcare services.

Institutes of higher learning have evolved to support the growing fields of gerontology and geriatric medicine. Educating the medical providers, workforce and community on the needs of older adults has become an area of profound interest within and outside of the academic environment. It is important to draw older people into the processes of developing the services and new technologies that they themselves and others of their generation will use. By developing these new healthcare opportunities, the greatest gains may be made in health, independence and quality of life (QOL) in old age.

Overview of healthcare demographics

The USA spends over 15% of the GDP, 2.5 trillion dollars, on healthcare expenditures. This is more than any other industrialized nation.[1–3] Healthcare expenditures have doubled in the past 10 years; however, 16% of population does not have health insurance. The provision of healthcare is equally split between private insurance, Medicare/Medicaid and other sources including out-of-pocket payers.

The annual number of hospitalizations has remained relatively stable at 11 per 100 population, and the average length of hospital admission has dropped consistently over the last 10 years to an average length of stay of 4.6 days.[3,4] Despite this trend, hospital expenditures have risen 50% in the last 10 years.[3] Outpatient encounters have increased by 40% over that same time.[4] About one-third of healthcare resources are spent on hospitalization and one-quarter on physician services. Individuals age 65 or older utilize one quarter of outpatient encounters, one third of hospitalization, and one third of the total healthcare expenditures.

Currently 13% of the US population is aged 65 or older. This population is projected to reach 21% by 2050.[5] These trends have caused great concern both economically and socially. The healthcare budget cannot sustain the current growth rate of medical expenditures. Methods to provide cost-effective, quality healthcare for an ageing population are being addressed on a system-wide level. Research funding, educational efforts and clinical care models are being developed to better serve the healthcare needs of the geriatric population.

Development of geriatric medicine

In the USA, geriatrics came into the medical consciousness through the writings of Dr Ignatz Nascher. Although born

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

in Austria, he was raised in the USA and received his medical degree from New York University. In 1909 at the age of 46, Dr Nascher published his first geriatrics article titled 'Longevity and Rejuvenescence'. In this work he proposes that 'geriatrics' be added to the medical vocabulary and that it be considered a distinct aspect in medicine. Over the next five years he authored more than 30 articles on ageing and the first American geriatrics textbook titled *Geriatrics: The Diseases of Old Age and Their Treatment*. This text focused dually on the physiology and pathophysiology of ageing. Nascher touched on a multitude of topics including organ system physiology, pharmacology, diseases of ageing, and psychosocial aspects of medicine. With an optimistic view, he wrote in 1926 that, 'Geriatrics is now firmly established as a special branch of medicine ... '.

Unfortunately, geriatrics was not yet widely accepted and the growth of this specialty was quite slow through the 1930s and 1940s. The mid-1900s were notable for the establishment of two medical societies. Malford W. Thewlis founded the American Geriatrics Society in 1942, and the Gerontological Society (now called The Gerontological Society of America) was established in 1945.

Research in ageing was championed by Dr E. Vincent Cowdry who received his PhD in anatomy from the University of Chicago in 1913. During his 65-year career spent predominantly at Washington University School of Medicine, Dr Cowdry focused his research efforts on cancer and the cytological changes of ageing. During the latter half of his career he authored several books including *The Problems of Ageing: Biological and Medical Aspects* (1939), *The Care of the Geriatric Patient* (1958), and *Aging Better* (1972).

Geriatrics in the United States developed as much through the establishment of governmental socioeconomic programmes as it did from the work of prominent physicians. In 1861, a military pension plan was established to support the Civil War era veterans. After the Civil War, many states established veterans' homes to provide disability and medical care services. These services were consolidated through the development of the Veterans Administration in 1930. By 1935, a rapidly increasing population of impoverished older adults led to the formation the Social Security Board which reorganized in 1946 to become the Social Security Administration. This programme provides a retirement benefit to individuals upon leaving the workforce. Although state and federal subsidies for healthcare services were sporadically available in the 1920s, the first private hospital insurance plan (Blue Cross) was not provided until 1933. Further discussion and development of government-sponsored health insurance for the elderly spanned five presidential administrations and more than three decades.

In 1950, through efforts by President Truman, the Federal Security Administration held a national conference on ageing to assess the challenges posed by the changing population. No immediate programmes were initiated, but this conference spurred the development of an advisory committee on ageing that eventually lead to the first White House Conference on Aging in 1961. The conference resulted in the expansion of Social Security benefits and support for the later development of Medicare and Medicaid. In 1965, insurance was finally guaranteed to older adults, the disabled and the impoverished through the passage of Medicare and Medicaid programmes.

During the mid 1900s, the US Government was the primary financial sponsor of healthcare research and scientific programmes. The National Institute of Health (NIH) was formed in 1930 and later became a consortium of institutes and centres dedicated to healthcare research. The National Institute on Aging (NIA) was formally established out of the National Institutes of Health (NIH) in 1974, but the roots of the NIA can be traced back to the 1940s and 1950s with the Unit on Aging, Gerontology Branch, and Section on Aging subsections of NIH programmes.

The NIA receives substantial funding for the advancement of ageing research. Through NIA support, the 30 Alzheimer's Disease Centers, 15 Claude D. Pepper Older American Independence Centers, and numerous Edward R. Roybal Centers for Research on Applied Gerontology sponsor investigations into the biological, behavioural and clinical aspects of ageing.[6,7] During the last quarter century, there has been a growth in the private support of geriatric medicine research and education. Hundreds of millions of dollars have been provided by The John A. Hartford, Donald W. Reynolds and other agencies dedicated to the care of the ageing population.

Home healthcare

For most of history, medical care has been provided in the home by a physician. In the mid 1900s 40% of all patient–physician encounters took place at home. With the growth of hospital and office-based care, fewer than 1% of healthcare visits took place at home by 1980.[8] Home healthcare (HHC) began growing again in the 1980s as new models of home assessment developed and the delivery of home care evolved into an organized, multidisciplinary business. The current HHC model primarily utilizes nursing, therapy and personal care providers to deliver healthcare services; however, physician house calls still remain under-utilized as a means of caring for frail older adults.

Home visits are an effective method for delivering medical assistance for the aged and chronically ill homebound individuals. House calls have most often demonstrated benefit in chronic and relapsing diseases such as congestive heart failure and emphysema. Regular visits by a medical professional can improve disease control and reduce hospitalizations.[9,10] This translates to a societal

cost savings, which has prompted Medicare, Medicaid and private insurance agencies to continue the funding of home care services.

Medicare and Medicaid provided nearly 80% of HHC coverage in the US between 1990 and 1997, HHC expenditures grew almost sixfold to $18 billion. The growth of HHC utilization prompted a change in reimbursement from a fee for service to a prospective payment system reimbursement model. Despite the change in funding, the expenditure on HHC has continued to increase and has more than doubled since 1997.[11] For each 60-day certification period, agencies are reimbursed around $2300 per enrollee, adjusted for geographic region and intensity of care provided.[12] This initially resulted in a reduction in the enrolment length and frequency of HHC visits, but over the past several years, the number of home healthcare recipients has increased. In 2007 nearly three million individuals received over 114 million home care visits from 9000 certified agencies.[13–15]

To qualify for HHC, an agency must receive a physician order, document that a recipient is homebound (a definition that has remained vague) and provide a skilled intervention by a nurse or therapist. Common uses of HHC include medication management, disease assessment, wound care, home safety evaluation, physical and occupational therapy, and patient/family education. The average number of visits per enrollee is 37.[14]

When personal care is needed at home, aides can be hired for in-home assistance with laundry, housekeeping, meal preparation and personal care needs. Medicare does not pay for personal care aides, nor do most private insurance plans. Individual case management and social services are available to seniors based on resources and needs. Services such as meals-on-wheels, transportation, and legal aid are often provided on a sliding fee-scale basis. The availability of these services varies by community.

Hospice care is another service traditionally provided in the home, although there is a growing use of hospice in the nursing home setting. In 2009, over 5000 hospice agencies provided care to 1.5 million individuals through Medicare, an increase of 20% over four years. Forty percent of these patients were served at home and 19% resided in nursing homes. Eighty percent of hospice recipients are age 65 or older and just over half are female. The average length of service is 69 days but 34% of hospice recipients die within 7 days of enrolment. This suggests that hospice services are largely under-utilized for those deemed to have 'less than 6 months to live'.[15] In addition to nursing, hospice provides therapy, social service and family support in the home. Hospice agencies are not capable of providing continuous 24-hour personal care.[15,16]

British physician Dame Cicely Saunders first coined the term hospice in 1967. Yale School of Nursing Dean Florence Wald subsequently adopted this care model in the United States. It was not until 1979 that the Health Care Financing Administration (HCFA) funded 26 hospices as a demonstration programme. In 1982 hospice care was added as a benefit under the Medicare and Medicaid programmes and has since become a standard benefit provided by all health insurance plans. To qualify for hospice a physician must certify an estimated life expectancy of six months or less. Half of the hospice enrollees have a terminal diagnosis of cancer. Cancer diagnoses have dropped 10% in the last three years due to a rise in use of hospice care for non-malignant terminal illnesses such as dementia and emphysema.

Nursing home care

The number of nursing homes in the United States has dropped slowly since the early 1980s, although the total number of residents in nursing homes has increased almost 10% during that time. In 2004 the number of licensed nursing home beds dropped to 1.7 million from 1.9 million in 1999. The average bed capacity increased slightly to an average of 108 residents per facility.[17] Seventy percent of nursing home residents are female and 85% are Caucasian. The average length of stay is 2–3 years. Despite common misconceptions of the elderly population, less than 5% of citizens over the age of 65 reside in nursing homes. Less than 20% of adults over age 85 live in nursing homes.

Most nursing homes certify a portion of their beds (25–35%) for post-acute care, skilled nursing services. These residents receive intensive nursing, therapy and medical services after an acute medical illness with the hope of regaining lost function. Medicare funds most of the skilled nursing care in the United States but private insurance also covers post-acute rehabilitation services. Medicare beneficiaries receive up to 100 days of skilled nursing care before other insurance or private pay must shoulder costs. The average length of skilled nursing care is 27 days.

Medicare and most private insurers do not pay for non-skilled (custodial) care in nursing homes. The bulk of custodial care is paid for by Medicaid once individuals have 'spent down' their personal resources to the point of qualifying for this jointly state-federal sponsored healthcare coverage. The Medicaid qualification level varies by state. An individual generally must have a monthly income less than or equal to the federally designated poverty level ($902/ month in 2010) and net personal resources of only a few thousand dollars.[18] The average yearly cost of nursing home care is roughly $70 000.[19] Nursing home insurance is becoming available but in general is costly and is not widely purchased by the general population.

Nursing home care has improved dramatically in the past 20 years. The Omnibus Budget Reconciliation Act (ORBA), passed in 1987, was instrumental in changing the management and oversight of nursing home care in the United States. Unfortunately, past abuses have resulted in

a highly regulated and punitive system of ensuring the current quality of institutional patient care. Nursing homes are surveyed annually by the State regulatory agency. Deficiencies and fines are applied liberally and are a matter of public record. The State has the authority to immediately close down any facility that is found to have practices that place residents in 'immediate jeopardy' of harm. Areas that are frequently cited include unnecessary use of physical restraints and psychotropic medication, weight loss, development of pressure ulcers and fall-related injuries.

As hospital length of stay shortens and the severity of illness of newly admitted residents increases, nursing homes have become more comprehensive in providing medical and therapy services. Most facilities offer intravenous antibiotics and fluids. Gastric tube feeding, suctioning and oxygen treatment are routine. Facilities contract with mobile laboratory and radiology agencies. Physical, occupational and speech therapists, nutritionists and consulting pharmacists are on-staff or consult on a regular basis. Nurses are being challenged to perform more sophisticated care and more rigorous assessments while faced with limited staffing ratios and a high rate of nursing turnover.

Assisted living facilities are assuming some of the role that nursing homes played 20 years ago. 'Well' elderly who require only some assistance with daily activities live semi-independently in studio-type apartments with or without a kitchenette. Facilities vary in size from several dozen to over one hundred residents in a single building. A licensed nurse is usually available during most of the day and may pass meds, perform assessments, inject insulin, check glucoses and perform other skilled tasks based on resident needs. The provision of meals, light housekeeping and social activities is usually included in the cost of room and board.

The cost of care is partly based on the level of services designated by the patient/family. Assisted living costs are highly variable but range from $30 000–40 000 or more per year.[19] Almost universally, the cost of assisted living is incurred out-of-pocket by the resident and/or family. Despite being less costly, most long-term care insurance providers will not reimburse assisted living as an alternate to nursing home care. Assistance with ADLs, IADLs, safety checks and other personal care are provided by 24-hour per day nursing assistants at the facility. At this time 900 000 residents reside in approximately 40 000 assisted living facilities. Most assisted living residents receive medical care in the office of medical providers as opposed to on-site as in nursing homes. There are currently very few governmental regulations or requirements in assisted living facilities.

Hospital care

Hospitals in the United States are evolving to provide specialty services for the ageing patient with the hope of improving patient outcomes and reducing adverse health events. Programmes such as adult day care, palliative care and home healthcare, offered through the hospital system, address a wide variety of needs for elderly patients both during and after hospitalization. The American Hospital Association (AHA) publishes the prevalence of these services annually. Over time, utilization of hospital-based skilled nursing units has dropped and use of free standing post-acute skilled nursing facilities has increased.[20] This is likely a result of decreased reimbursement of in-hospital skilled nursing care. In the subsequent years, the frequency of hospital-based services for care of older adults has declined steadily as seen in Table 143.1. The only geriatric programmes which have increased significantly, are palliative care and case management with 28.8% and 80.6% of hospitals having these services respectively in 2007.[21,22] It is interesting that neither an Acute Care for the Elderly (ACE) unit nor a stroke unit are used as markers in this consumer-evaluation model, but both are accepted by the field of geriatric medicine as beneficial interventions.

ACE units

The ACE unit is a growing model for comprehensive and multidisciplinary care of the older hospitalized adult. An ACE unit is a hospital-based ward which emphasizes a comprehensive, multidisciplinary approach to acute care of older adults. These units are usually associated with a university hospital, 15–20 beds in size, and admit patients with a variety of medical conditions.[23] The 'ACE' concept and term were developed in the early 1990s with key elements of the model being (1) environment alterations, (2) patient-centred care, (3) interdisciplinary planning for discharge, and (4) medical care review. Important components of an ACE unit structure are detailed in Table 143.2.[24] The goal of this model is to reduce the functional impairments which so often develop in acutely ill, hospitalized elders.

Table 143.1 Hospital facilities and services trends.[21,22]

Special services offered	% of hospitals 2007	% of hospitals 2003
Skilled nursing care unit	28.5	33.4
Intermediate care unit	9.8	10.2
Adult day care services	6.2	8.1
Assisted living	4.5	5.3
Case management	80.6	75.5
Geriatric services	38.4	40.4
Home health services	32.7	37.4
Hospice	23.5	23.3
Meals on wheels	10.4	12.8
Psychiatric-geriatric services	29.4	30.4
Palliative care programme	28.8	22.2

Table 143.2 Components of an Acute Care for the Elderly (ACE) unit.

Interdisciplinary Team
Medical Director
Physician
Nursing staff
Social work/Case management
Pharmacist
Pastoral care
Palliative care
Therapy services
Physical
Occupational
Speech
Dietician
Regular team meetings
Daily updates
Interdisciplinary participation
Daily assessment
Physical
Cognitive
Functional
Specialty geriatrics training/education
Staff
Patients/families
Physicians
Comprehensive discharge planning
Home discharge emphasis
Coordination with home care services
Communication with caregivers
Assessment for geriatric syndromes
Delirium
Dementia
Depression
Polypharmacy
Falls
Incontinence
Functional decline
Frailty
Environmental modifications
Communication aids
Reorientation strategies
Restraint reduction protocols
Assistive devices
Sleep hygiene
Higher nurse:aide ratio

Two philosophical differences are employed in the ACE model of care. First, care management is shifted toward a biopsychosocial rather than a biomedical model. The hospitalization and discharge planning process focuses on the relationship between the patient and the social structures that are needed for effective treatment. Barriers to successful recovery and risks for ongoing functional decline are identified early in the hospitalization. Appropriate interventions such as reduction in polypharmacy, nutritional assessment, social support evaluation, and physical and occupational therapy assessment are initiated for each patient. Discharge plans ensure that the patient transitions to an appropriate environment and with appropriate social services in place.

Second, a functional-based rather than disease-based approach is used in medical decision-making. Many elders suffer from multiple, chronic medical conditions that will not be cured. Goals of care focus on maximizing function in the context of disease management rather than solely marking improvement by measures of disease severity. With this method, functional status and QOL measures become the markers for successful recovery from illness.

The implementation of an ACE unit has consistently resulted in improved functional status and increased discharge to home compared with usual care wards.[24–26] Despite the additional interventions applied by the multidisciplinary team, the total cost of hospital care is not higher on the ACE unit. The benefits of teamwork in caring for the complexity of frail older adults translates to a more efficient and thorough treatment plan for both the hospital and the patient, without resulting in excess cost. Despite these potential benefits, the growth of ACE units and research in this area has not increased substantially in the past 5–10 years.

Stroke units

Death from cerebrovascular disease is the third leading cause of death and more than two-thirds of strokes occur in patients over the age of 65. Despite longstanding use of stroke units outside of the USA, and strong evidence demonstrating the morbidity and mortality benefit of this strategy, comprehensive stroke management models are just beginning in the US healthcare system.[27,28] Previous literature on the benefit of an organized inpatient stroke care team comes almost universally out of the United Kingdom and Northern Europe. For over 20 years, patients with acute stroke in these countries have been managed on a dedicated stroke unit: either on a discrete stroke ward or by a stroke team working exclusively with stroke patients. The focus of a stroke unit can include acute stroke care, subacute rehabilitation or a combination of strategies.

To improve the consistency and quality of stroke care across the United States, the 'Brain Attack Coalition' (BAC) was convened in 2000 to establish recommendation for hospital care of stroke patients. The BAC recommended a two-tier organization for hospital-based stroke care: Primary Stroke Centres (PSCs) and Comprehensive Stroke Centres (CSCs). The major criteria for a PSC or CSC are listed in Table 143.3.[29] PSCs provide the basic emergency

Table 143.3 Requirements for Stroke Centre Certification.[29]

Primary Stroke Centre	Comprehensive Stroke Centre
Acute Stroke Team 24-hour coverage 15-minute response time	Expert Personnel Vascular specialists Neurology Neurosurgery Surgery
Written Protocols Diagnostic steps Therapeutic steps	Interventional Specialists Radiology Neuroradiology
Emergency Medical Services (EMS) Coordination with hospital Communication during transport	Advance Practice Nurses Stroke nurses Critical Care Physicians Physiatrists
Emergency Department Trained staff Coordination with Stroke Team Coordination with EMS	Rehabilitation Therapists Physical Occupational Speech Respiratory
Stroke Unit Specialized monitoring Specialized services	Invasive Therapies Carotid endarterectomy Aneurysm treatments Reperfusion therapies
Neurosurgical Services Available within 2 hours	Infrastructure Stroke unit Intensive care unit 24-hour coverage 24-hour operating room Interventional services Stroke registry
Commitment Hospital administration Medical staff	Diagnostic techniques MRI with angiography CT with angiography Cerebral angiography Transcranial Doppler Carotid ultrasound Transoesophageal echo
Neuroimaging CT scanning with 25 minutes Radiology review within 20 minutes	Educational Programmes Community Professionals Patients
24-hour Diagnostic Services Laboratory ECG X-ray	
Quality Improvement Stroke registry Outcome database	
Annual Educational Programmes 8 hours staff continuing education 2 community programmes	

evaluation and stabilization, while complex cases requiring specialty imaging and intervention should be referred to a CSC. Although over 600 hospitals have accreditation as a PSC, this represents less than 15% of US hospitals.[30]

Academic geriatrics

The development of academic geriatric programmes and medical training has lagged behind the demand for a larger and more skilled geriatric medicine healthcare workforce. This is in part due to the lack of universal acceptance of Geriatrics as a unique discipline within the medical profession. With the increasing age, functional impairment and psychosocial complexity of older adults, the mantra that 'I'm a geriatrician because most of my patients are elderly', is fading, but slowly.

In 1982, Mount Sinai School of Medicine established the first Department of Geriatrics. At this time most of medical

schools have some form of a geriatrics programme. The vast majority of the 132 academic geriatrics programmes are organized as Divisions or Sections within a Department of Internal or Family Medicine.[31] Few institutions have the financial capability of supporting independent departments of geriatric medicine. Two thirds of geriatrics programmes have been in existence for less than 20 years. The average programme has 10 faculty members. Fifty percent of programme leaders have been in that position for less than eight years.[32] The first professorship in geriatric medicine was granted at Cornell University in 1977.

Dr Les Libow at Mount Sinai School of Medicine offered the first geriatric medicine fellowship programme in 1966. Since that time the number of trainees and training sites remained fairly limited until the early 1980s. In the 1970s, the Veterans Administration was charged with the task of increasing the understanding of ageing and passing this knowledge to healthcare providers. Funding was provided in 1975 for the first VA Geriatric Research Education and Clinical Center (GRECC). Twenty GRECCs are currently active through the VA.[33] GRECCs began offering geriatric medicine fellowship training opportunities in 1978.

In 1988 the Accreditation Council for Graduate Medical Education began accrediting geriatric medicine fellowship training programmes. 1988 was also that year that an examination became mandatory to attain the Certification of Added Qualification (CAQ) in Geriatrics after at least two years of fellowship training. Until the mid 1990s, most fellows in geriatric medicine engaged in two or more years of training. Extended training was vital for the development of an academic and research career in geriatrics. In 1995, the training requirement for CAQ in geriatrics was reduced to one year and geriatric medicine became an independent subspecialty with board certification status.

Currently there are 105 Internal Medicine and 45 Family Medicine accredited geriatric medicine fellowship training programmes.[34] Despite an increasing number of medical student graduates in the United States, almost one third of fellowship slots go unfilled each year. Although the number of fellowship training programmes has increased, the total number of board certified geriatricians and number of graduates from fellowship training have not increased substantially in the past 10 years. There is significant concern that the increased need for geriatric specialists will not meet the population needs in the next two decades. Significant changes in the healthcare structure and workforce will be needed to ensure that adequate care for older adults can be provided in the US healthcare system.

Conclusion

In the next 50 years, the population demographic in developed countries will change substantially. Up to a quarter of the citizens will be over age 65 with the highest growth rate in age seen in the oldest age groups. Older adults are the highest consumers of healthcare resources and are usually supported, at least in part, by local and national governmental medical programmes. With healthcare costs rising, the United States continues to explore alternate means of caring for the ageing population.

Home healthcare includes a wide variety of programmes and services, most of which are not physician-directed. Traditional physician house calls remain a small portion of the home care encounters performed today. The provision of medical and non-medical services allows individuals to remain independent and in their homes for a longer period of time. Many services are community based and thus help individuals maintain a connection with society.

Nursing home care has increased substantially in cost and complexity over the past 20 years. In an effort to control escalating long-term care costs, intermediate care settings have evolved to allow individuals more autonomy in a less costly setting. Resources and supervision are provided to individuals on an as-needed basis in most of these facilities. For individuals in need of comprehensive supervised care, nursing homes still provide the maximal degree of therapy, social work and nursing support.

Hospital care has evolved to focus more on the delivery of quality healthcare to the elderly individual. Stroke units are well established as an effective model for managing hospitalized older adults. ACE units are now growing in the same manner. It is apparent that quality care for complex elderly patients requires a team of medical providers working together toward common goals.

Academic geriatrics has grown substantially over the past 50 years with most medical schools and academic centres establishing a department or section of geriatric medicine. The role of geriatricians, relative to general practitioners, is still evolving in the care of the older adult. As the older population expands there is an ongoing need to training physicians, both generalists and specialists, in the principles of geriatric medicine.

Key points

- The elderly will account for over 20% of the US population in the next half century.
- Services for the elderly have grown most extensively in the realm of home healthcare.
- Geriatric wards, stroke units, and Acute Care for the Elderly (ACE) units are well-developed and effective models of hospital care for the elderly.
- The growth of nursing home care has slowed and is shifting to 'intermediate-care' service models.
- Geriatrics as a unique field of medicine has developed over the past half century.

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CHAPTER 144

Systems of healthcare: Australia

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Overview of healthcare demographics

Australia has an ageing population comparable to most developed countries. In 2005, 13.1% of the 20 million residents were age 65 and over. With a life expectancy of 79.2 for males and 83.7 for females, it is estimated that one quarter of the Australian population will be over age 65 by the year 2051. At that time, the projected life expectancy will be 83.3 for males and 86.5 for females. In this population, dementia is the leading cause of disease burden by a factor of two. Dementia accounts for 16.7% of years of life lost to disability. Currently, over 160 000 Australians have dementia and this rate is predicted to increase over 250% by 2041. While vascular disease and cancer remain the two leading causes of death, mortality rates from these diseases in older people have decreased markedly over the last decade.[1]

While the health of the Australian population has generally been improving, the health of indigenous people, the Aborigines and Torres Strait Islanders (ATSI) has not improved at the same rate. These groups suffer death rates of two to three times that of the general population. The leading causes of death in these individuals remain vascular disease, respiratory illness, injury and cancer. While aged care services for most Australians are targeted toward the population over age 70, for ATSI people these same services are provided for those over age 50.

Australia spent 9.8% of the GDP on healthcare in 2004–2005 (AUD $87.3 billion). Although health spending has grown as the population has aged, this is mainly attributed to spending on new technology and pharmaceuticals, rather than on the increasing number of older individuals. The percentage of GDP spent on healthcare is lower than the United States, comparable to Canada and European countries, but higher than the United Kingdom. The Australian health system is tortuous in its complexity, particularly for the consumer. The services and care for older adults have been particularly complicated.

Development of geriatric medicine

The speciality of Geriatric Medicine in Australia is generally considered to have started in 1950 when the Hospital Commission of New South Wales (NSW) requested the Royal Newcastle Hospital to survey the known people with multiple sclerosis in the Hunter Valley, with a view to setting up a hospital clinic for those patients. Dr Richard Gibson and Miss Grace Parbery, a social worker, were appointed to conduct the survey and identified the need for medical, nursing and domestic care at home for the chronic sick in general. It took another five years to institute these outreach services and subsequently hospital rehabilitation services as well. Rudimentary services started soon after in other states but the independent origins led to different patterns of development.

Australia was founded in 1901 as a federation of six states each of which had a slightly different history and health system. Each state government retained control of existing health services, mainly hospitals. Over the years, the growth of national government taxation revenue has resulted in the introduction of new healthcare programmes, mainly non-hospital services. Many of these services were developed in response to genuine healthcare deficiencies but as a result, Australia has a dually administered health system through a partnership of the national and state governments. The Australian National Government generally retains primary control over the newly established healthcare services or programmes. The national government pays for community health, nursing home and visits to doctors' offices, but the level of control over these programmes varies. The Australian Government pays for visits to doctors under the Medicare scheme of universal health insurance. Medicare is partially funded by a 1.5% levy on income tax and a 1% surcharge from those earning at least AUD $50 000. Additional revenue for the physician may be generated from the patients, who are responsible for paying

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when the physician decides to charge an extra fee. Medicare reimburses physicians 85% of the established *Schedule Fee*, an amount derived from a survey of fees in the early 1970s. The schedule fee has been under-adjusted for inflation over time, with a resulting 30% drop in reimbursement rates. This has prompted some physicians to pass on increasing co-payment fees to their patients. At this time, the percentage of GP consultations entirely paid for by Medicare has declined to about 70%.

Most medical care for older people is administered by GPs. Medicare disproportionately rewards GPs for shorter office-based consultations, which favours younger, single problem patients. General practice has also seen a shift toward corporatization, where companies employ GPs in multidoctor practices and generally discourage non-office work. These trends have resulted in a decrease in the number of GPs who perform home or nursing home visits. In 1999 a range of longer, better-remunerated consultations were introduced to encourage adequate consultations with frail, older people, including annual health assessments, multidisciplinary care planning and case conferencing. These have recently been augmented to also cover residential aged care; however, these measures have not been adequately assessed to determine whether they provide any benefit.

The Australian Government under the Pharmaceutical Benefits Scheme (PBS) pays for medications with some co-payments charged to patients. Rapid increases in the cost of the PBS of around 15% per year have led to a variety of measures to decrease costs. One method is to limit the number of new drugs coming onto the PBS. Patients have also been required to pay the full cost of many new drugs. In other situations, drug companies will negotiate to cap payments for a new pharmaceutical agent on the basis of the projected medication expenditures for that agent.

Geriatric Medicine is a relatively new, but growing speciality. A survey of all specialist consultant physicians found that there were 185 practising geriatricians in 2003. One third also practises general medicine. This provides Australia with approximately one geriatrician per 5900 people aged 75 and over.[2,3] Because geriatric medicine attracts a higher proportion of female specialists in Australia, and over a lifetime, females work approximately 75% of the hours of male graduates, access to geriatricians is more limited than what is actually calculated. The demand for geriatricians is increasing, but not currently met by the supply of trainees. In 2007 specific long and comprehensive consultations exclusively for geriatricians were introduced which meant that a geriatrician could be reimbursed by Medicare at a higher rate than any other physician, to appropriately reflect the complexity of consultations with frail older patients.

The profession, healthcare industry and the government continue to grapple with this problem.

Home healthcare

Home care services have become increasingly complex in the types of care provided, the funding arrangements, and number of service providers. The healthcare needs of patients are also more complex due to greater functional and physical dependency. Medical care at home has traditionally been provided by GPs for patients who were too acutely or chronically unwell to attend office visits. However, the relatively poor reimbursement by Medicare and the increasing demand for home visits has led many GPs to abandon them altogether. Because many aged care assessment teams (ACATs) now include a geriatrician or other medical officer, they may provide medical home visits as part of an initial assessment, but not as part of routine care.

Government-sponsored community services existed as early as the 1940s, including emergency housekeeper service and meals-on-wheels, delivered by women volunteers on bicycles. The Australian Government began funding home nursing services in 1956. Although the management and structure varies considerably between states, there is general availability of visiting registered nurses to provide nursing services in the home. Most commonly these services are time limited and based on the individual needs of the client and family. There are separate but generally parallel services for war veterans and individuals in the private sector. Home and Community Care (HACC) services expanded in 1969 to support housekeeping or other domestic assistance, senior citizens centres and welfare officers. Home care was further enhanced with the passage of the Home and Community Care Act in 1985 to include personal care such as bathing and dressing. Demand almost perpetually outstrips supply, because of under-funding, lack of gate keeping at entry, and inadequate exit strategies for maintenance services. A common assumption by service providers is that clients will not significantly improve and thus need prolonged enrolment in the programme. Home care recipients assume that services are difficult to access and thus attempt to retain services long term rather than re-request assistance at a later date.

HACC also funds meals-on-wheels, transportation, home maintenance and modification, counselling, social support, centre-based day care, allied health services, provision of aids, respite care and laundry. HACC services are not exclusively for older people, with 23% of their clients being under age 65, but usage rates do increase with age. The most commonly used service is domestic assistance (usually housekeeping). In 2007–2008, 8 million hours of domestic assistance were provided under the HACC programme. The programme was jointly funded by the state (40%) and national government at $1.65 billion in 2007–2008.

ACATs are a network of 128 regionally based multidisciplinary teams that provide comprehensive geriatric assessment at home or in hospital, facilitate access to

the best possible combination of services at home, and determine eligibility for residential and complex community care. ACATs often provide health advice and support for the common conditions, which afflict older people, such as dementia and incontinence. ACATs may assume the additional therapeutic role of rehabilitative therapy. ACATs assess approximately 1 in every 10 people over age 70 every year. ACATs have a key role in assessing older people at home in complex situations, such as when elder abuse is suspected or if guardianship is being considered. If residential placement is recommended, the ACAT works with the client and their caregiver to negotiate entry. Staffing varies but generally includes nursing and allied health, social workers, physiotherapists, occupational therapists and psychologists. Increasingly ACATs have access to a geriatrician, particularly when they are co-located with a hospital aged care service, and sometimes even a psychogeriatrician. In non-metropolitan areas, the medical officer is usually a GP (family medicine practitioner) with an interest in aged care.[4]

Referral to ACAT is from any source, including self-referral. ACATs perform a standardized initial assessment using a minimum data set, with subsequent assessments according to identified problems. Occasionally, ACATs must assess younger people with disabilities for eligibility to enter residential aged care if no suitable alternatives exist. The shift away from institutional care has led to ever more complex packages of care being introduced into the community. The Community Options Programme was established in the late 1980s to provide case management and brokerage funds in the community to a small group of clients that is up to 10 times the average level of funding for other HACC clients, and also as recognition of the wide range of services available in the community.

Community aged care packages (CACPs) were introduced in 1992 and support people at home with up to 14 hours of care per week as a substitute for admission to a hostel. Assistance with personal care such as bathing, domestic assistance with laundry, shopping, meal preparation, gardening and transportation outside the home are provided. The median length of time on the programme is just under a year. Two-thirds of people who leave the programme are admitted to residential care or die. More than half (56%) of all recipients live alone and only 8% live with their children. Recipients pay up to $7.69 per day, with the Australian Government providing $35.41 per day per recipient.

Extended Aged Care at Home (EACH) packages were introduced in 1998 to support people at home who are eligible for nursing home placement. Clients receive an average of 16.1 hours of care per week. These recipients tend to be younger (32% under age 75) and more cognitively intact (31% diagnosed with dementia, compared to 80% in nursing homes) than most nursing home residents. The government subsidy for EACH Dementia packages is $130.54 per day. The more complex packages of care require ACAT assessment of need.[5] By June 2006, about 48 000 people were receiving CACP or EACH packages with the governments plan to make available 18 CACP per 1000 persons over the age of 70. By comparison, over 236 000 were staying in residential aged care, although 37 000 were there temporarily in respite care.[6]

Transition Care Programmes (TCP) commenced in 2005 to provide up to 12 weeks of care for frail older people who had not recovered sufficiently, after an acute hospital stay and usually some rehabilitation, to manage independently at home and thereby were at risk of permanent institutionalization. The National Evaluation suggested that TCP reduced the risk of entering an institution (hospital and residential aged care) during six months of follow-up.

Although the spectrum of home care appears broad and comprehensive, it can also be cumbersome and complex. In practice, 17 separate programmes are funded by the Australian Government and delivered by a myriad of 4000 different service providers. Most state governments fund additional services, particularly for post acute care at home after hospitalization. The result is a complicated health delivery system with patchy coordination and insufficient communication, particularly for consumers and their caregivers. In theory, one assessment by ACAT should be sufficient for any other service but, in practice, each service provider makes its own assessment. That this plethora of providers does not meet the needs of older disabled people and their caregivers was demonstrated by a study of dementia sufferers in Victoria. Data revealed that over 40% of demented individuals do not make use of any community or respite services. When asked why they did not make use of various community services, 77-88% of individuals stated that the services were not needed, although many caregivers were not managing well as evidenced by poor self-reported health and high levels of strain.[7] Since 1972, caregivers have been subsidized by a domiciliary nursing care benefit to care for a disabled person at home who would otherwise require institutional care. The patient must be over the age of 16 and certified by a medical practitioner to require continuing care.

Nursing home care

The development of residential aged care dates back to the poor houses of the nineteenth century. In NSW, the first state, government asylums for the aged and destitute were built to house the aged poor. By 1890, these homes had become ‘practically hospitals for chronic and incurable diseases as well as homes for the infirm and indigent’. However the introduction of a pension plan in 1909 allowed more aged poor to continue living in the

community and institutional care was used only for marked disability or poverty.[8] Essentially all residential care was provided by the charitable and public sectors until the mid-1950s, but not-for-profit organizations still provide 63% of all residential care places.

In 1954, there was a swing back to residential aged care when the Australian government passed the Aged Persons Homes Act that provided subsidies to charities (and later to private operators) that built or purchased homes for needy older people. This prompted a surge in construction of nursing homes that continued for three decades. In the early 1970s, a quota of 50 nursing home beds per 1000 population of age 65 and over was introduced. An intermediate level of care, called *hostel*, was announced in an attempt to reduce the number of nursing homes being built, particularly by the private sector. Hostels were aimed at people who needed assistance with IADLs while nursing homes were designed for people who needed assistance with basic ADLs. A 1978 survey found that 30% of nursing home residents could easily be treated at home with minimal services.[9] In 1986, a government review pointed out that the cost of institutional care had risen tenfold in 10 years, from $100 million to $1 billion per annum, and the percentage of the Department of Health's budget paid to nursing homes had increased from 9 to 25% over 20 years. By the mid 1980s nearly 90% of all aged care funding was going to residential care. The rate has now been reduced to about 75% with a commensurate increase in community care. In 2004, there were 175 000 allocated residential care sites and 30 000 community care sites. On the basis of the truism that most people prefer to remain in their own homes, the government changed the quota for nursing home beds to 72.6 per 1000 people over age 70. In 1985, the multidisciplinary ACATs were charged with developing more stringent entry criteria, which resulted in a 35% decrease in admissions to nursing homes. HACC services were also strengthened in order to maintain people at home.[10] Over the years, the government has changed the ratio of nursing homes and hostel places to increase the availability of home support, but this has been complicated by the growth of the population over age 70. Individuals over age 85 are most likely to require nursing home placement and are the fastest growing segment of the population. A decrease in funding for residential care has caused many facilities to close down. Ninety licensed residential care beds are now allocated per 1000 population over age 70. These transformations have meant significant increases in disability in hostel care, as well as increased average disability in nursing homes.

A further series of reforms took place in 1997 with the introduction of the Aged Care Act. The two levels of care were unified under one legislative framework with an integrated Resident Classification Scale (RCS) and quality assurance framework. The levels were renamed high (nursing home) and low (hostel) care. The 1997 reforms also introduced a small amount of deregulation and emphasized greater contributions to the cost of health and welfare services by those with the capacity to pay. In general, the provision of residential aged care remains a controversial issue in Australia. Approximately one in three people who reach 65 years of age will spend some time in residential aged care, but whether the cost should be met more by the community or by the individual and their family is a matter of equity, ethics and finances.

Hospital care

In 1993, a government survey of 942 Australian hospitals found that 32% operated a geriatric service. These were almost exclusively based in the public sector, and usually consisted of visiting care services.[11] Only 13% of programmes included a geriatrician. Replication of the survey in 2001 found that 31% of 778 hospitals had a geriatrician providing inpatient care.[12]

The distribution of geriatric services varies between states. Those states with more acute geriatric medical beds typically provide care to patients admitted through the emergency department. New South Wales, Western Australia and South Australia have the highest ratio of acute geriatric beds (0.67–0.85 beds per 1000 people over age 70 in 2002). In Victoria and Western Australia there are more designated aged care rehabilitation beds (0.62–0.63 per 1000 people) than in the other states. The extent of geriatric services vary by hospital, with 11% reporting a day hospital, 7% having bed-based psychogeriatric services, and only 4% having orthogeriatric services. Orthogeriatric services provide coordinated orthopaedic and geriatric management for older traumatic and elective orthopaedic patients. The type of geriatric services available to patients tends to mirror the hospital environment. Where the hospital focuses on acute-care and managing emergency admissions, more attention is devoted to improving assessment and management of older people in the emergency department and on acute hospital wards. Where the hospital has developed a stand-alone rehabilitation centre, more emphasis is placed on managing chronic conditions, such as dementia, Parkinson's disease and incontinence. However, with time the scope of available services is increasing and differences between states are receding.

Stroke units are becoming increasingly popular, although geriatrician involvement is not universal. A recent study found that only 40% of all strokes were treated in stroke units.[13] Hospital in the home for older patients is increasing in popularity, but is essentially in its infancy as a model of healthcare. This service provides patient-centred care in the patient's home or a residential care facility, while decreasing the risk of hospital associated adverse events.

Major geriatric complications were less likely to occur in the hospital in the home model compared with the traditional hospital model.[14]

Public hospitals, which are the majority, are under the control of state governments.

Only about 30% of hospitals are private and these concentrate on elective procedures. Almost all large and teaching hospitals are public, so that the vast majority of acute and more complicated medical or surgical work is done in public hospitals. Admission to a public hospital as a public patient is free to Australian residents. However, if a patient wants a choice of doctor, they must enter as a private patient. Owing to tax incentives, about 43% of the population has private insurance for hospital care. Public hospitals receive about half their budget from the national government and half through the state governments.

This dichotomy of control of the health system has led to lack of coordination, and incentive to cost-shift between the hospital and non-hospital sectors. There are also limited health services run by local government (the third tier), religious and charitable organizations, individuals and private commercial interests.

Academic geriatrics

In NSW, geriatric medicine originated in the Royal Newcastle Hospital, an acute public hospital and later became an acute speciality hospital. Lidcombe Hospital in NSW was another early centre of geriatric medicine that evolved away from the mainstream, having originally been an asylum which developed into an acute hospital, but retained a large group of long-stay chronic patients. Many of the doctors involved there went on to be national leaders in geriatric medicine. In Victoria, South Australia, and Queensland the speciality started in chronic hospitals, which developed out of the poor houses, and continues as a rehabilitation hospital model, though it now also interacts with acute hospitals. In Victoria, the Mount Royal Hospital was a custodial institution for elderly people where the state hospital and charities commission decided to open a geriatric centre, aimed at rehabilitation. Though the initial director was only part-time, the centre flourished and also became a centre for ageing research. The Australian Association of Gerontology was formed in the early 1960s as a multidisciplinary organization interested in later life, and the doctors involved went on to form The Australian and New Zealand Society for Geriatric Medicine (ANZSGM) to meet the special needs of medical practitioners. Many geriatricians take a leading role as advocates for older people together with consumers and other service providers.

The Royal Australasian College of Physicians (RACP) recognizes geriatric medicine as a speciality. Trainees must complete 3 years of advanced training in geriatric medicine, though 1 year of this may include working in another speciality or in full-time research. Advanced training can only be undertaken after successfully completing the demanding written and oral basic physicians' examination, which is generally attempted 4–5 years post-graduation from medical school. Only about two-thirds of candidates are successful in this exam. Almost all basic physician trainees, who later go on to various internal medicine subspecialities, have some exposure to working in geriatric medicine. This is most beneficial for attracting trainees for advanced training. However, workforce issues are as much a problem in terms of shortages in the supply of doctors for older people, as well as nurses and allied health professionals.

The first full professor of geriatric medicine was appointed at the University of Melbourne in 1975, though early professorships were often in 'community medicine and geriatrics'. Now each medical school boasts of at least one professor and there are research institutes dedicated to age-related research in the larger states.

Many other research institutes also have some interest in age-related research. Clinical research is also conducted in many teaching hospitals. Most research funding derives from the National Health and Medical Research Council that does not yet have a section devoted to ageing. However, in 2002 the Australian Government released a national strategy for ageing research and identified national research priorities which included 'promoting and maintaining good health' whose goals include 'ageing well, ageing productively'. This led to the establishment of two research networks designed to encourage and seed fund collaborative interdisciplinary research into ageing.

Key points

- The speciality of geriatric medicine in Australia is generally considered to have started in 1950.
- Extended Aged Care at Home (EACH) packages were introduced in 1998 to support people at home who are eligible for nursing home placement.
- Geriatric medicine is a relatively new, but growing speciality. A survey of all specialist consultant physicians found that there were 185 practicing geriatricians in 2003. One third also practises general medicine. This provides Australia with approximately one geriatrician per 5900 people aged 75 and over.
- ACATs are a network of 128 regionally based multidisciplinary teams that provide comprehensive geriatric assessment at home or in hospital, facilitate access to the best possible combination of services at home, and determine eligibility for residential and complex community care.

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CHAPTER 145

Systems of healthcare: the United Kingdom

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Introduction

The growth in life expectancy at birth in much of the Western world reflects an ongoing revolution in longevity. This revolution encompasses both survival of individuals to older ages and changing age profiles of the entire population. In particular, the growth of the oldest old has resulted in significant healthcare changes, both on an individual and at societal level. Developed nations across the world have approached the ageing population and need for expanded health services in a variety of ways. Home health, hospital-based and nursing home care have experienced a profound increase in complexity of care needs over the last quarter century. This complexity of care is reflected in the expansion of funding arrangements, number of service providers and geographic service areas. Governments have expanded healthcare spending and broadened the scope of medical care. The development of health insurance programmes in some countries has allowed a greater number of individuals to access medical services. Institutes of higher learning have evolved to support the growing fields of gerontology and geriatric medicine. Educating the medical providers, workforce and community on the needs of older adults has become a major area of interest within and outside of the academic environment. It is important to draw older people into the processes of developing the services and new technologies that they themselves and others of their generation will use. By developing these new healthcare opportunities, the greatest gains may be made in health, independence and quality of life (QOL) in old age.

Overview of healthcare demographics

The proportion of UK citizens aged >80 years is set to increase from 2.7 million in 2008 to 6.7 million in 2050; at the same time the proportion of younger citizens will fall, with the result that the dependency ratio[1] will rise from 25% today to 38% in 2050.[1] By 2060, healthcare spending will take up 8.3% of gross domestic product (GDP), and long-term care 0.7% of GDP.[1] The rapid growth in the oldest old, with the associated frailty and the apparent failure to compress morbidity into the final year or two of life, means that the health and social care of frail older people will continue to be a major challenge for the UK Government.

Healthcare spending in the United Kingdom has grown more quickly than other economic expenditures, reaching 8.1% of the gross domestic product (GDP) in 2007. Even in the harsh climate of post-recession Britain, healthcare spending remains an important part of the overall UK budget, which continues to support publicly funded health and social care. Public healthcare expenditure increased by £5.1 billion (8%) in 2002 compared with £700 million (5%) in private health expenditures. All individuals residing in United Kingdom are entitled to receive treatment from the National Health Service (NHS), which is free at the point of delivery. The NHS, established in 1948, is the third largest employer in the world after the Chinese Army and Indian Railways respectively.

Development of geriatric medicine

For various historical reasons, specialist geriatric services developed as an integral part of the NHS in the United Kingdom earlier than in any other area of Europe. Marjorie Warren established geriatric medicine in Britain in the late 1930s. Her message was the need for assessment and rehabilitation of older disabled people, education of medical students, and research into the problems of ageing and old age.[2,3] This derived from her work in the workhouse infirmary associated with the West Middlesex

[1]The dependency ratio is the ratio of people aged 65+ in relation to people aged 15–64, expressed as a percentage.

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Hospital in London. Her methods (careful medical and social assessment, medical treatment and rehabilitation) were described in a series of publications.[2–4] The general conclusion was that older patients should be treated in a dedicated area of general hospitals because:

- geriatrics is an important subject to teach medical students;
- geriatrics should be an essential part of the training of student nurses;
- general hospital facilities are necessary for correct diagnosis and treatment;
- research on diseases of ageing can only be undertaken with the full facilities of a general hospital.

These were visionary proposals in 1943 but continue to resonate in current discussions about managing older people. The emerging recognition of the needs of older people in an ageing society led to a number of major surveys and resulted in the collection of planning data for the introduction of new healthcare services. Curran and colleagues (1946) published data on about 1000 males over age 65 and females over age 60 and who lived in poorer areas of Glasgow, all of whom received home visits. A social and medical survey of people in England over age 65 was also performed by the Nuffield Foundation in 1943. The results were published in two reports: *Old People* (1947) and the *Social Medicine of Old Age* (1948).[5,6] The British Medical Association (BMA) set up a working group in 1947 to review care of the elderly and infirm and to make general healthcare recommendations.[7] Of the 21 BMA members, four were active in the new speciality of Geriatrics (Amulree, Brooke, Cousin, Warren). Dr Trevor Howell, originally a general practitioner (GP), became interested in geriatric medicine after becoming responsible for Chelsea pensioners. He was appointed consultant physician at Battersea and subsequently opened one of the first geriatric units.[8–10] In 1947, he called a meeting to bring together physicians who had a special interest in older people and skills in rehabilitation, incontinence management and domiciliary assessment. This meeting launched the Medical Society for the Care of the Elderly, the society was renamed the British Geriatrics Society in 1959. These pioneering physicians persuaded the Minister of Health to appoint more geriatricians as part of the hospital consultant expansion of the new NHS. Dr Tom Wilson was appointed the first consultant geriatrician in 1948 at Cornwall, which marked the introduction of this new medical speciality. By 2008, there were 1111 consultant geriatricians in the United Kingdom, but increasing subspecialization (for example into stroke medicine) and the feminization of the workforce means that the long-term aim of having one whole time equivalent geriatrician per 40 000 of population is still some way off.

The NHS has recognized the value of Geriatrics, now the largest medical speciality in the UK, and has invested significant time and resources to improve services and standards of care for older people. During the 1980s and much of 1990s, the trend in United Kingdom was for geriatric practice to become more closely identified with acute general internal medicine and to be less involved with rehabilitation and long-term care. The improved access to acute diagnostic facilities for older people was welcomed. The rise in consumerism and desire for choice have resulted in the public having a higher expectation of all services. Inadequacies and inequalities in the healthcare of older people have had a major influence on current heath policy, now in part being addressed by the National Institute for Heath and Clinical Excellence (NICE – http://www.nice.org.uk/). A campaign started by a national newspaper and an older people's charity (Help the Aged) led the government to commission an independent inquiry into the care of older people. As a result of the finding, a National Service Framework (NSF) containing standards of care for older people was published in 2001 in order to apply to the NHS for implementation. The NSF was a 10-year healthcare improvement programme implemented through local health and social care partners, and national underpinning programmes. It was the first framework to establish standards for social as well as healthcare. The NSF established new national standards, service models and social services for all older people, whether they lived at home, in residential care or in hospital. This was achieved through the single assessment process, integrated commissioning arrangements and integrated provision of services. Ten years later, whilst there is still much to be done, the NSF has facilitated major improvements in the care of frail older people. In response to older peoples' demands for care close to home,[11,12] there is a growing move to shrink the acute hospital sector whilst increasing community services for older people. In the UK at least, it seems as though we have come full circle and are now rediscovering the art of geriatric medicine in community settings as pioneered by Marjorie Warren in the 1940s.

Home healthcare

The practice of seeing patients in their own homes has been an essential component of geriatric practice since its early stages when consultants inherited large panels of patients with long waiting lists. However, there has been something of a demise in domiciliary visits in the last decade, relating in part to the growing purchaser-provider split in the NHS. But as acute care episodes are shrinking, there is a growing need for geriatric expertise to support acute care in the community setting. This is especially true for intermediate care settings – either patients being 'stepped-up' from their own home to a more supportive environment in the context of a crisis (usually medical) or patients being 'stepped-down' from acute care (early supported discharge). Community services have developed massively in the last few years,

and include residential or home-based intermediate care, community matron services and other therapy and social services. Geriatricians are increasingly integrating with such teams to deliver comprehensive geriatric assessment.

In addition to services aimed at supporting medical and social crises, there are a growing number of falls prevention services and other out-patient type activities being provided in the community, which traditionally would have been delivered in hospital outpatients or geriatric day hospitals. Despite their popularity with staff and patients, day hospitals have come under increasing pressure to close as they are perceived as being too expensive.

Psychogeriatric services have developed along the lines described above, with reciprocal roles in the acute and community sector, and the recent focus on expanding memory clinics. However, acute hospital care for people with mental health issues in non-psychiatric settings is significantly underdeveloped. More recently there is a growing interest in developing dedicate units for patients with mental health issues, analogous to the development of stroke and orthogeriatric services.

Preventive care in the community rests very much in the hands of general practitioners, with focused efforts to increase the uptake of vaccinations and screening for common treatable conditions such as diabetes and hypertension. Access to falls services remains somewhat *ad hoc*, though NICE guidance does request that older people are asked about falls with a view to accessing falls prevention services. Older people are currently excluded from the common cancer screening programmes (colorectal cancer and breast cancer), but this is being hotly debated and may change.

There is a growing awareness of the benefits of exercise in older people, not just in terms of preventing falls and functional decline, but also for the psychological and metabolic benefits. A great deal of work remains to be done to identify the optimal methods of engaging older people (as well as younger people!) in healthy living activities.

Nursing home care

The care home sector in the UK has largely taken over the role of the long-term care wards from the 1940s. There are around 5700 nursing homes in England providing 186 800 beds. Individuals admitted to nursing homes tend to be heavily dependant and require regular nursing care (for example for care of pressure sores). Individuals in residential homes will require some help with activities of daily living, but should not require daily access to nursing care. In practice there is considerable overlap within homes, as many are registered to provide both nursing and residential care. There are dedicated nursing homes for those with psychiatric disorders, including dementia, which may also be registered to provide residential care. All state-funded individuals should now undergo a continuing care assessment prior to entry into long-term care to determine their need for nursing care.

The majority of care homes are in the hands of the private sector, with most being run as a relatively small business with no more than 20–30 residents. Healthcare input is variable, and it is not unusual for residents in one care home to be managed by their original general practitioner, rather than a single GP service taking over the care of all residents. This results in rather fragmented care and relatively little support for social care staff who are left managing the most complex, frail older people. This may in part explain the substantial number of care home residents admitted to acute care with a crisis that might have been reasonably managed in the care home had the support mechanisms been in place. It is interesting to contrast a UK care home with models such as those used in Holland, with larger units and greater medical and therapy input.[13]

The ideal approach to the comprehensive management of care home residents would see a collaborative effort between the geriatricians and the GP providing day-to-day care in the nursing home setting in conjunction with other health and social care professionals. However, geriatricians have been criticized for a relative lack of attention to the long-term care and community-based care needs of frail older people. Greater attention is now being focused on care home medicine.[14] Newer models (or the re-birth of old models) such as interface geriatrics[15] – combining acute hospital geriatrics with community geriatrics are starting to emerge.

Hospital care

Various models of acute hospital care exist throughout the UK, ranging from age-based services (though these are becoming less and less prevalent following the focus on ageism in the NSF), needs-related (based on geriatric syndromes) or a more integrated approach. A common goal is to discharge patients (sometimes too quickly) from such wards either to their own homes or to other appropriate settings. Patients requiring ongoing nursing care for irremediable conditions are referred for nursing home admission.

A major factor in the delivery of acute hospital care is the European Working Time Directive, which mandates the number of hours that a doctor can work in a single day and over a week. Most hospitals now operate a shift system, with a loss in continuity of care. Despite efforts to improve medical handover of patients, there is still significant disruption. Older people, especially those with cognitive impairments, may suffer more at the hands of this new system than their more autonomous younger counterparts. Given that older people occupy around two-thirds of all hospital beds, this raises major concerns about

the quality and by inference the efficiency of acute hospital care. On a more positive note, multidisciplinary working is now widespread, not just within geriatric medicine units. Overt age discrimination is rare and will soon be the subject of legislation, but subvert age discrimination in the form of inadequate assessments and the attribution of functional decline to age rather than a medical diagnosis remains a major challenge to be tackled.

One of the areas of geriatric medicine that has perhaps had the greatest success (some might argue to the detriment of other areas) is stroke medicine. Stroke medicine has gone from being a cinderella speciality to becoming a priority, both in hospital care (through the provision of thrombolysis services and acute stroke units, etc.) and in primary care (early supported discharge and daily access to clinics for patients with possible transient ischaemic attacks).

Academic geriatrics

The first academic chair of Geriatric Medicine was established in 1965 in Glasgow, Scotland. The first professor of geriatric medicine was William Ferguson Anderson (1914–2001). There is concern amongst some geriatricians that conventional academic geriatric posts are withering on the vine[16] and that opportunities for funding geriatric research, as opposed to ageing research, are inadequate. This view is fuelled by concerns that many chairs in Geriatric Medicine have been 'lost' or remain unfilled. Combined with concerns about undergraduate geriatric education,[17–19] might lead one to become despondent about the future of any would-be academic geriatricians. But there are now around 50 geriatricians holding professorial chairs throughout England and Wales, and many geriatricians hold important roles in undergraduate education throughout the country, albeit not necessarily university-based posts. Now, more than ever before, Geriatrics is the mainstream speciality. Geriatricians are no longer seen as second-class physicians, but are becoming increasingly valued for their generalist approach and ability to manage complex patients, whether in acute care settings, rehabilitation settings, in end-of-life care and other scenarios both in primary and secondary care. Few other specialities can bring such breadth of knowledge and skills to their patients. Teaching of the geriatric giants is now commonplace on most medical school curricula. Several geriatricians have leading roles in the Royal College of Physicians and the Department of Health as well as other august bodies. In terms of research, ageing is now one of the top three priority areas for the Medical Research Council, and the rationalization of NHS funding should lead to a greater focus of research on priority areas for the NHS – of which ageing and frailty is surely one.

Higher medical training in geriatric medicine is well established, and there are currently around 400 trainees nationally. Applicants for higher medical training (HMT) should have completed a minimum of two years general professional training and have to pass a competitive interview to enter further medical training before choosing a speciality (Figure 145.1)

Clinical training in geriatric medicine is usually undertaken in parallel to training in general internal medicine and lasts five years. There are dedicated training structures for clinical academics which can take longer. Whilst such clear pathways are to be welcomed, they do rather impose an early choice on relatively junior doctors (Figure 145.2), which may be a concern for geriatric medicine – typically a mature or late choice for career physicians.

Conclusion

In the next 50 years, the population demographic in developed countries will change substantially. Up to a quarter of the citizens will be over age 65 with the highest growth rate in age seen in the oldest age groups. Older adults are the highest consumers of healthcare resources and are usually supported, at least in part, by local and national government medical programmes. With healthcare costs rising, countries like the United Kingdom, United States and Australia are exploring alternate means of caring for the ageing population. Home care encompasses a wide variety of programmes and services, most of which are not physician-directed. Traditional community geriatrics dropped substantially in the early 1990s and despite a recurrence in interest, is still nascent. The provision of medical and non-medical services should allow individuals to remain independent and in their homes for a longer period of time. Many services are community based and thus help individuals maintain a connection with society. As the ageing population expanded, health expenditures increased tremendously. In an effort to control escalating long-term care costs, intermediate care settings have evolved to allow individuals more autonomy in a less costly setting. Resources and supervision are provided to individuals on an as-needed basis in most of these facilities. For individuals in need of comprehensive supervised care, nursing homes still provide the maximal degree of therapy, social work and nursing support. Hospital care has evolved to focus more on the delivery of quality healthcare to the elderly individual. Stroke units are well established as an effective model for managing hospitalized older adults. ACE units are now growing in the same manner. It is apparent that quality care for complex older patients requires a team of medical providers working together toward common goals. Academic geriatrics has grown substantially over the past 50 years with most medical schools and academic centres establishing a department or section of geriatric medicine. The role of geriatricians, relative to GPs, is still evolving in the care of the older adult. As the

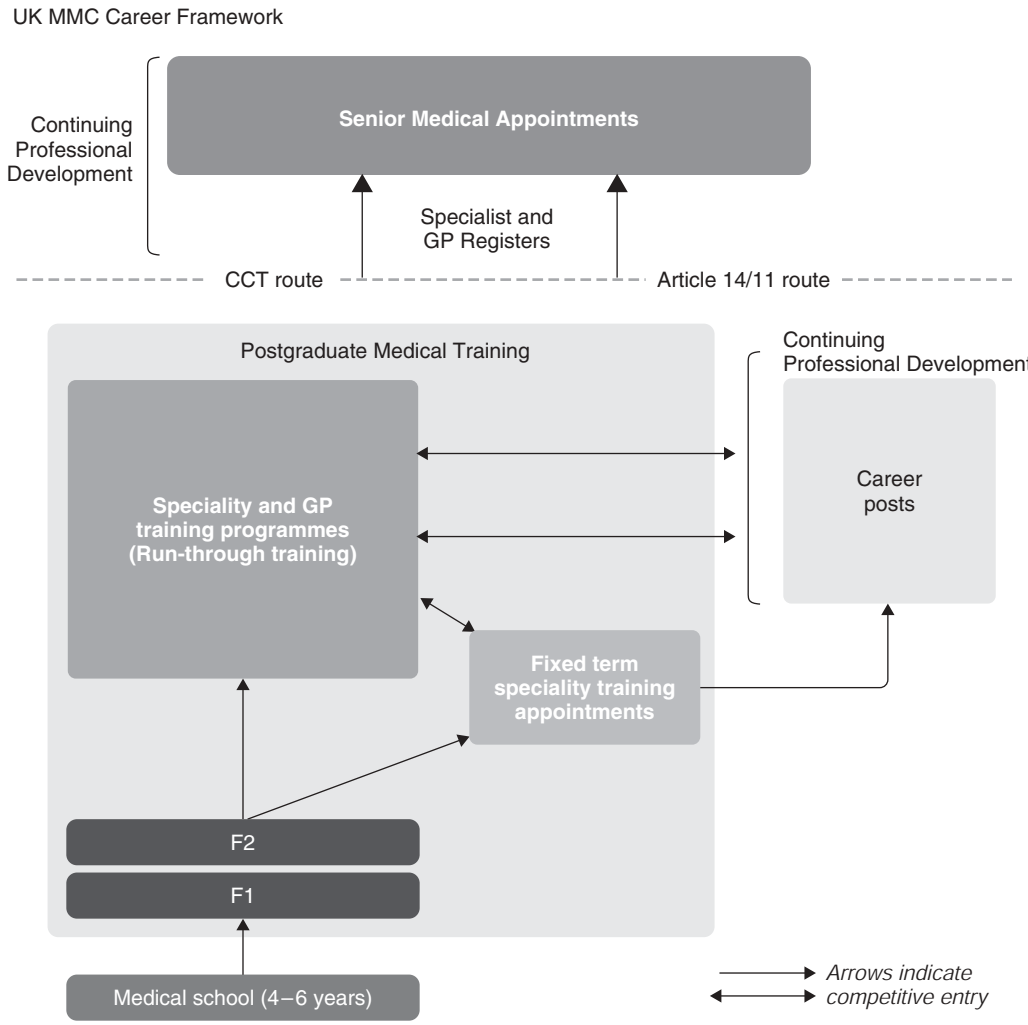

Figure 145.1 Training structure for medicine in the United Kingdom.

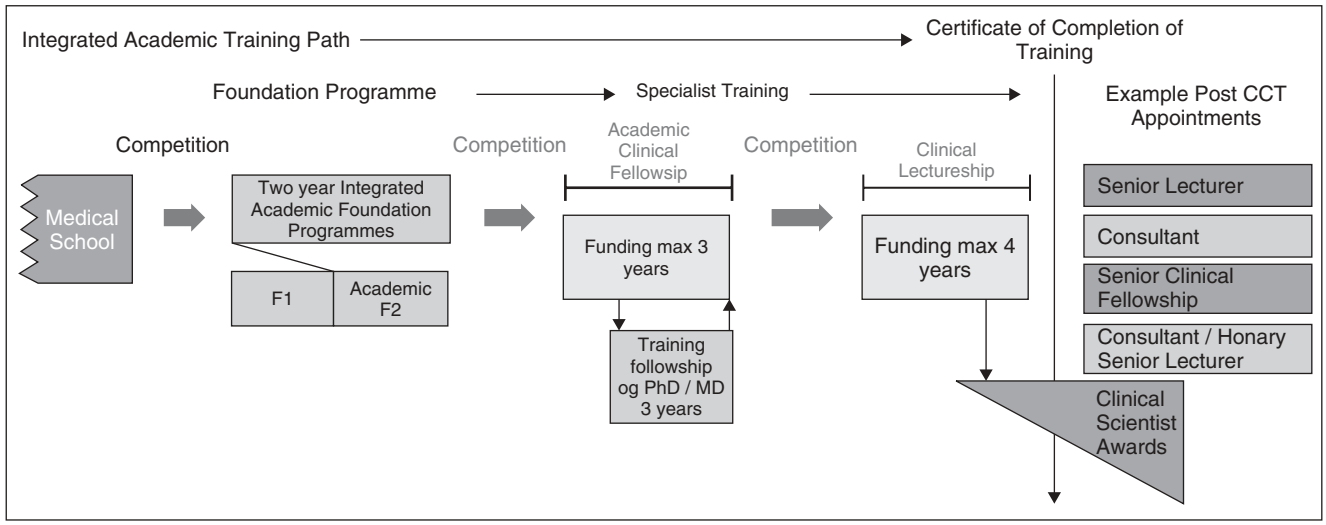

Figure 145.2 Academic training in the United Kingdom.

older population expands there is an ongoing need to train physicians, both generalists and specialists, in the principles of geriatric medicine.

Key points

- Older people will account for over 20% of the United Kingdom, United States and Australian population in the next half century.
- Services for older people have grown most extensively in the realm of home healthcare.
- Geriatric wards, stroke units and Acute Care for the Elderly (ACE) units are well developed and are effective models of hospital care for older people.
- The growth of nursing home care has slowed and is shifting to 'intermediate care' service models.
- Geriatrics as a unique field of medicine has developed over the past half century.

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CHAPTER 146

Geriatric medicine in China

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Introduction

The elderly population in China

China is a developing country. It has undergone a rapid economic growth recently, and is now the world's third-largest economy. In the past 60 years, China has made great achievements in controlling infectious diseases and improving public health. A direct indicator is the demographic transition from a young population into an ageing population. In 1999, the proportion of elderly people aged 60 years and over was already more than 10%. In the 5th National Population Census of 31 provinces, autonomous regions and municipalities of mainland China in November 2000, the population was 1 265 830 0010. There were 88 110 000 persons aged >65 years. This represented 7% of the population.[1] In the 2005 One-percent Population Survey, the total population of China was 1 306 280 0010. The number of persons >65 years had increased to 100 450 000, which constituted 7.7% of the whole population. In 2005, average life expectancy at birth was 71.0 years for males and 74.0 years for females. (Tables 146.1, 146.2 and 146.3).[2]

There are several special features regarding population ageing in China. The number of elderly is huge and represents 20% of the world's elderly population and 50% of the Asian elderly population, and the growth is rapid. From 1982 to 1999, the proportion of elderly persons aged >60 years increased from 7.64% to 10.1%. Such a demographic transition occurred within 18 years in China but the same change took several decades in developed Western countries. China has now moved into an accelerated phase of population ageing and is becoming an ageing society in an underdeveloped economy. While Western countries have become both 'old' and 'rich', China has become 'old' before getting 'rich'. This constitutes a burden on economic growth. Another characteristic is the regional difference in the demographic transition. Population ageing occurs more rapidly in the developed coastal cities than in the underdeveloped inner rural areas within China. Urban cities show a higher proportion of elderly people than rural areas. For example, in 2005 Shanghai had the highest percentage of elderly people (11.94%) while Qinghai province had the lowest (6.04%).[2] Amongst elderly population subgroups, the growth of those aged >80 years is fast and increasing at a rate of 5.4% per year. This subgroup increased from 8 million in 1990 to 11 million in 2000 and is projected to reach 27.8 million by 2020.[1,3] With an ageing population, the prevalence of chronic diseases, which include diabetes mellitus, hypertension, stroke, coronary heart disease and chronic obstructive pulmonary disease, has also increased. For example, 1.5 million patients are newly diagnosed with stroke every year in China. Heavy medical expenses are required and these diseases constitute an important burden. Although the life expectancy of women is higher than men, women survive longer but are less healthy than men.[1–6] The birth control and one-child policy has had a great impact on family size in China.[7] The Chinese family has decreased from 4–5 to 3–4 person households in recent years. Family size is largest in rural areas and small in city areas. This trend has been affecting the foundation of traditional family support of the elderly population.

The elderly population in Hong Kong SAR, Macau SAR and Taiwan

In 2009, 0.89 million persons in Hong Kong were aged 65 years and over, which represented 12.8% of the total Hong Kong population. The proportion of Hong Kong elderly will increase to 26.4% by 2036.[8] This increase will place an enormous demand on long-term care and healthcare services. The ageing demographic change is related to a decrease in births in Hong Kong.[9–12] The elderly dependency ratio, which is defined as the number of persons aged 65 years and over per 1000 persons aged 15–64 years, will increase from 382 in 2001 to 562 in 2031. In 2009, average life expectancy at birth was 79.5 years for men and 85.2 years for women (Tables 146.1, 146.2 and 146.4). Life expectancy is closely related to the healthcare needs of the elderly. In 2009, at age 60, the average life expectancy was 22.3 years

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Table 146.1 China's population (including Hong Kong SAR, Macau SAR, Taiwan).

	Mainland China (1 Nov. 2005; One-percent Population Survey)	Hong Kong SAR (2009)	Macau SAR (2008)	Taiwan (2009)
Total population	1 306 280 0010	7 003 700	549 200	23 069 000
No. of elderly (>65 years)	100 450 000	893 500	39 500	2 406 097
% of elderly (>65 years)	7.69% (Increase of 0.73% compared with 2000 Census)	12.8%	7.19%	10.43%
Average life expectancy at birth, years	All = 73.0		All = 82.0	
	Male = 71.0 Female = 74.0	Male = 79.5 Female = 85.2	Male = 79.0 Female = 84.8	Male = 75.6 Female = 81.9

Table 146.2 China major cities' population in 2005, Hong Hong in 2009.

	Beijing (2005)	Shanghai (2005)	Hong Kong SAR (30 June 2009)
Total population	15 360 000	17 780 000	7 003 700
No. of elderly (>65 years)	1 660 000	2 120 000	893 500
% of elderly (>65 years)	10.79% (increase of 2.37% compared with 2000 Census)	11.94% (increase of 0.48% compared with 2000 Census)	12.8% (increase of 1.8% compared with 2000 Census)

Table 146.3 Declining birth and death rates in mainland China.

Year	Mainland China (Overall)		Beijing		Shanghai	
	Natural birth rate (per 1000 pop.)	Natural death rate[a] (per 1000 pop.)	Natural birth rate (per 1000 pop.)	Natural death rate[a] (per 1000 pop.)	Natural birth rate (per 1000 pop.)	Natural death rate[a] (per 1000 pop.)
1949	36	20	–	–	–	–
1970	33.43	7.6	–	–	–	–
1980	18.21	6.34	–	–	–	–
1990	21.06	6.67	13.35	5.43	11.32	6.36
2001	13.38	6.43	6.1	5.3	5.02	5.97
2002	12.86	6.41	6.6	5.7	5.41	5.95
2003	12.41	6.40	–	–	–	–
2006	12.09	6.81	6.26	4.97	7.47	5.89

[a]Natural death rate=crude death rate

for men and 26.9 years for women, and at age 80, this was 8.3 years and 10.6 years for men and women, respectively. The increased life expectancy is related to improvements in public health and nutrition, and also to improved medical care for very elderly patients.[8–12] However, improved survival may not mean normal health without disability or functional impairment. Elderly persons have multiple chronic diseases, functional impairments and need for regular medical services.[13–15]

Macau SAR is a small city in China. In 2008, it had a population of 0.55 million. The natural birth and death rates have fallen over recent decades and the population is also ageing. In 2008, the elderly aged >65 years constituted 7.19% of its population. Average life expectancy at birth for males and females was 79.0 years and 84.8 years, respectively (Tables 146.1 and 146.4).[16]

Taiwan has also experienced a rapid demographic transition. The fertility rate has decreased from 5.9 children per woman in 1949 to 1.77 in 1997. Thus, the ratio of adult children to older parents will fall greatly in the coming years. A decline in the death rate has resulted in an increase in average life expectancy at birth. Between 1951

Table 146.4 Declining birth and death rates in Hong Kong SAR, Macau SAR and Taiwan.

Year	Hong Kong SAR		Macau SAR		Taiwan	
	Natural Birth Rate (per 1000 pop.)	Natural Death Rate (per 1000 pop.)	Natural Birth Rate (per 1000 pop.)	Natural Death Rate (per 1000 pop.)	Natural Birth Rate (per 1000 pop.)	Natural Death Rate (per 1000 pop.)
1946	20.1	20.1	–	–	–	–
1956	37.0	37.0	–	–	–	–
1966	25.5	25.5	–	–	–	–
1976	16.9	16.9	–	–	–	–
1986	13.1	13.1	–	–	–	–
1990	12.0	5.2	20.5	4.4	15.5	5.6
1995	11.2	5.1	14.1	3.2	13.8	5.7
2000	8.1	5.1	8.8	3.1	11.7	5.7
2002	7.1	5.0	7.2	3.2	11.0	5.7
2003	6.9	5.4	–	–	–	–
2006	9.5	5.5	–	–	–	–
2008	11.3	6.0	5.4	3.2	8.6	6.2

and 2008, average life expectancy at birth has increased from 53.4 years to 75.6 years for males, and from 56.3 years to 81.9 years for females. These changes have led to an increase in the elderly population (>65 years) from 2.5% in 1950 to 10.4% in 2008. This percentage is projected to increase to 24% by 2030. The increase of those aged 80 and over is very fast. In 1960, 9.2% of the elderly population belonged to the >80 group. By 2036, almost one-quarter (24%) of the elderly population will be in this group.[17–19] (Tables 146.1 and 146.4).

Policies toward ageing in mainland China

Officially, the basic principle of China's ageing policy is to maintain sustainable development by setting up a support system partnership involving the state, community, family and the individual. The priorities in meeting the challenge of population ageing in China are to develop China's economy, to set up an old age security system, to speed up the establishment of a community-based care system, to set up a legislative system to protect the rights of the elderly (the Law of the People's Republic of China on Protection of the Rights and Interests of the Elderly was enacted in 1996), to establish safety networks for the elderly, to raise their living standards, and to create an environment for healthy ageing. In the past decade, China has set up five guiding principles for the work on ageing. These are 'Elderly people should be supported, have medical care, be contributive to society, be engaged in life-long learning and live a happy life'. In 1994, the China Development Outline on the Work of Ageing was formulated with a view to gradually upgrading living standards of the elderly and to enrich their cultural life.[20]

As formal care services are limited, many older persons rely on the support of family members, particularly in rural areas. Family support functions include financial support (income security), care-giving tasks (physical care) and comforting tasks (psychological care). Most of the younger population still maintain that taking care of elderly family members is their responsibility. However, more and more young people are unable to provide all of these functions, and require some assistance from the government, policy-makers and community services providers.[4,6]

It is projected that the rapid ageing in China will lead to only 2 working-age people for every senior citizen by 2050, compared with 13 to 1 now. Pension support is of great concern. As of March 2008, the Chinese pension system covered 205 million people, which represents 15% of the population. In rural areas, the pension system started in 1990 and covers only about 10% of the rural labour force. A further one-third drop in the number of pension participants occurred between 1999 and 2004. This was a setback attributed to the government's shortsightedness, as it was assumed that families would take care of rural elderly. Family support is declining, as younger family members migrate to work as labourers in factories, construction sites or other employment in cities. There is a plan to expand urban and rural pension coverage which aims at changing the present system to help migrant workers who change jobs frequently to maintain their retirement benefits.[21] There are other initiatives, including four 'demonstration bases' in the cities of Beijing, Tianjin and Chongqing, and in Jiangsu Province. The total investment would amount to 500 million yuan (Chinese dollars) each year. These centres would provide a model for the industry on care for the elderly. With regard to public commitment to long-term care, there will be an

increase in the number of nursing homes. For example, Beijing plans to add 15 100 nursing home beds in 2010, that is, an increase of 43%.[21]

Health of the elderly in mainland China and Hong Kong SAR

In mainland China in 2008, the top killer diseases included cancer, cerebrovascular diseases, respiratory diseases, heart diseases, injuries and poisoning. Chronic diseases included hypertension, cerebrovascular diseases and coronary heart disease (CHD). Diabetes mellitus and CHD are more common in urban city areas than in rural areas.[22–25] (Table 146.5). All these fatal and chronic diseases occur predominantly in elderly persons.

In the Hong Kong SAR, the top killer diseases in the elderly include cancer, heart diseases and pneumonia,[12] while common chronic diseases include arthritis, hypertension and diabetes mellitus[13,15,27–30] (Table 146.6).

Healthcare services in mainland China

China's healthcare delivery system is organized in a three-tier fashion. In urban areas, it consists of street health stations, community health centres and district hospitals. In the economically less-developed rural areas, village stations, township health centres and county hospitals are responsible for healthcare delivery. Doctors in the village stations receive only six months training (i.e. no formal medical school) after junior high school and receive an average of 2–3 weeks ongoing education every year. Township health centres usually have 10–20 beds and are looked after by a physician with 3 years of medical school education after high school. They are supported by assistant

Table 146.5 Causes of death and common chronic diseases in China (all ages), 2008.

City	County
Top killer diseases in 2008:	**Top killer diseases in 2008:**
Male	*Male*
1 Cancer	1 Cancer
2 Cerebrovascular diseases (stroke)	2 Cerebrovascular diseases (stroke)
3 Heart diseases	3 Respiratory diseases
4 Respiratory diseases	4 Heart diseases (incl. HT heart disease)
5 Injury and poisoning	5 Injury and poisoning
6 Diseases of the digestive system	6 Diseases of the digestive system
7 Endocrine, nutrition and metabolic diseases (e.g. diabetes mellitus (DM))	7 Endocrine, nutrition and metabolic diseases (e.g. diabetes mellitus (DM))
8 Kidney diseases (nephritis, nephrotic syndrome, etc.)	8 Kidney diseases (nephritis, nephrotic syndrome, etc.)
Female	*Female*
1 Cancer	1 Cerebrovascular diseases (stroke)
2 Heart diseases (incl. HT heart disease)	2 Cancer
3 Cerebrovascular diseases (stroke)	3 Respiratory diseases
4 Respiratory diseases	4 Heart diseases (incl. HT heart disease)
5 Injury and poisoning	5 Injury and poisoning
6 Endocrine, nutrition and metabolic diseases (e.g. diabetes mellitus (DM))	6 Endocrine, nutrition and metabolic diseases (e.g. diabetes mellitus (DM))
7 Diseases of the digestive system	7 Diseases of the digestive system
8 Kidney diseases (nephritis, nephrotic syndrome, etc.)	8 Kidney diseases (nephritis, nephrotic syndrome, etc.)
Common chronic diseases:	**Common chronic diseases:**
1 Hypertension	1 Hypertension
2 Diabetes mellitus	2 Gastroenteritis
3 Cerebrovasclar diseases	3 Rheumatoid arthritis
4 Coronary heart disease	4 Intervertebral disc disease
5 Intervertebral disc disease	5 Cerebrovasclar diseases
6 Gastroenteritis	6 Chronic obstructive airway disease
7 Rheumatoid arthritis	7 Choleltih and cholecystitis
8 Chronic obstructive airway disease	8 Diabetes mellitus
9 Choleltih and cholecystitis	9 Coronary heart disease
10 Peptic ulcers	10 Peptic ulcers

Source: Ministry of Health of China. *China Health Statistics* [Abstract], 2008.[25]

Table 146.6 Mortality and morbidity of the elderly in Hong Kong.

Leading causes of death in the elderly in 2001:

1 Cancer
2 Heart diseases (incl. HT heart disease)
3 Pneumonia
4 Cerebrovascular diseases (stroke)
5 Chronic lower respiratory disease
6 Kidney diseases (nephritis, nephrotic syndrome, etc.)
7 Diabetes mellitus (DM)
8 Injury and poisoning

Common chronic diseases:

1 Arthritis
2 Hypertension
3 Bone fracture
4 Peptic ulcers
5 Diabetes mellitus
6 Coronary heart disease
7 Hyperlipidaemia
8 Dementia
9 Hyperthyroidism
10 Chronic obstructive airway disease
11 Stroke
12 Asthma

Source: Chu, 1998[13]; Woo, 1997[15]; Chiu, 1998[27]; Chu, 2005[28]; Lau, 1997[29]; Leung, 1997[30]

physicians and village doctors. County hospitals usually have 250–300 beds and are staffed by physicians with 4–5 years of medical training after high school. They are assisted by nurses and technicians.[5,22,31]

Healthcare costs in old age are an important problem for the poor and those living in rural areas. If they cannot afford the costs, they will be denied access to healthcare. In the olden days, the rural Cooperative Medical System (CMS) schemes primarily provided funding and organized prevention, primary care and secondary healthcare for the rural population. After 1950, a mutual assistance mechanism was established to provide access to basic drugs and primary healthcare. During the Cultural Revolution (1966–1976), the CMS was given a political priority. The rural CMS then organized health stations, paid village doctors to deliver primary healthcare, provided drugs and partially reimbursed patients for services received at township centres and county hospitals. China's relative success in extending healthcare to the rural population has played a key role in improving the health status of the population. However, the CMS suffered from problems of poor management and a small risk-pooling base, contributing to the downfall of these early cooperative financing schemes after the initiation of agricultural reforms in 1980. The CMS has gradually disintegrated in most rural areas. In 2004, fewer than 10% of China's villages had a CMS scheme. In addition, many village doctors have left to go into farming or to become private practitioners. Township health centres and county hospitals are largely financed by fee-for-service and out-of-pocket payment. Access to healthcare in many areas is principally governed by the ability to pay rather than the need for healthcare. Many elderly persons in villages face bankruptcy if they have a major illness and have to be hospitalized. For example, the cost of one average hospitalization would exceed the average annual income of 50% of the rural population. The insurance coverage level of the primarily village-based community financing schemes in rural areas is severely limited. Poverty after an illness and the related treatment expenses continues to be a serious problem for the rural elderly, and they are often deprived of the needed medical care because of their inability to pay. Reform of the rural CMS is needed. In May 1997, the State Council issued a special document emphasizing that CMS reform was a major direction for China's rural health reform.[31]

The healthcare costs of elderly retired government officials or workers from large corporations are paid from either the Government Insurance Scheme (GIS) or Labour Insurance Scheme (LIS), which have been effective in ensuring equity of access to healthcare. In urban areas, GIS and LIS will pay the healthcare costs for most elderly persons. Exceptions are those who do not belong to these two groups, who have to be financed by fee-for-service and out-of-pocket payment. Again, access to healthcare amongst these persons is determined by the ability to pay. In recent years, the government and other enterprises are facing increasing difficulty in supporting GIS and LIS medical expenditures. With the rapid introduction of high-technology medical services, increasing incomes drive up the demand for healthcare. Without an effective controlling mechanism on the medical service consumers or providers, China now faces a serious problem of inflation in medical costs. The primary weaknesses of GIS and LIS programmes are the relative inefficiency in health resource allocation and healthcare provisions as well as the lack of risk-pooling across enterprises or local governments. Each organization under GIS and LIS systems is self-insured. If an enterprise is running a deficit, it will not be able to reimburse the medical expenses of the employee or the retired employee, rendering the individual uninsured.[6,31]

Healthcare for the elderly requires government provision and support. However, the distribution of healthcare resources including healthcare professionals in China is very uneven. Geographical variations exist between cities and rural areas as well as coastal and inland areas. Eighty percent of healthcare resources are allocated to the cities, of which two-thirds are allocated to big hospitals. Primary health organizations in rural areas are severely insufficient. The healthcare utilization rate is very low, largely related to inadequate supply and access. The level of healthcare

resources in mega-cities like Beijing and Shanghai may match those in developed countries. However, primary healthcare has not adequately developed. The charging system for healthcare is through insurance from government for government officials and for employees of large companies. These are also applicable to retired older persons who have previously worked in government institutes or major companies. Ordinary elderly people without these insurance supports have to pay the medical costs out of their own pocket. A government financial subsidy policy is usually not available, which is not reasonable.[31]

Healthcare financing reforms have recently started in some pilot cities. In 1994, Jiujiang in Jiangxi Province and Zhenjiang in Jiangsu Province were selected as pilot reform cities. A combination of individual saving accounts and social risk-pooling formed the basis for financing medical expenditures. This model emphasized individual responsibility with social protection through citywide risk-pooling for GIS and LIS. These reforms had some success in controlling the escalation of medical costs and in expanding coverage to those who were previously uninsured or underinsured. In 1996, it was decided that the pilot scheme should be extended to over 50 cities in 27 provinces and administrative regions.[31]

The coverage and financing of healthcare has been an ongoing difficult problem in China. Realizing the weaknesses of the public Government Insurance Schemes (GIS) and the Labour Insurance Scheme (LIS) the Chinese Government combined the two schemes into one. Currently, 180 million urban employees are covered under this new scheme.[32]

Since 2003, a new rural cooperative medical scheme (NRCMS) has also been launched in rural areas. This is essentially a basic health insurance scheme. In the ensuing five years, this scheme became increasingly adopted by citizens in rural areas, and by September 2007, 730 million rural citizens were included. A similar version of basic health insurance was also implemented in city and town areas. By 2007, over 30 000 000 persons were covered by this scheme.[24,32]

Community health services

According to the Chinese National Committee on Ageing, China has limited resources to set up comprehensive facilities to meet the increasing needs of the elderly. However, community service is considered to be an attractive way to complement the role of the family in caring for elderly persons. Over the past decade, there has been a great development in community service. By 1997, there were 930 000 community service facilities, 5055 community centres and 1.01 million community service stations throughout the whole country. Eighty-five percent of these facilities primarily serve the elderly persons in the local community, and 5.4 million volunteers have provided services. The community service embraces several groups of service providers including care services for daily living (e.g. home help, lunch, household work, shopping, escort, etc.), cultural activities (e.g. activity centres, lifelong learning, universities of the third age), legal assistance (i.e. when the legal right of an elderly member is violated) and day care services. Day care services are provided by either homes for the elderly or day care centres. The latter also provide simple medical services like clinical check-ups, intravenous saline treatment (as 'health maintenance') and family hospital beds. The medical service components are derived from the earlier street health stations and community health centres in urban areas. 'Doctors' in these centres usually receive basic training only and do not have formal geriatric medicine training.[33]

The Chinese Government's most pressing concern is how to provide equal access to basic healthcare for all Chinese people. Implementing basic medical and healthcare services for all would include public health, rural healthcare services, urban community healthcare services, and traditional Chinese medicine. Increasing the commitment of the central, provincial and local governments must be achieved. Development of basic healthcare facilities with basic medical technology, training for basic healthcare manpower, and making the basic drugs available to all urban and rural residents should be implemented. These reforms should also include changes in healthcare financing. Government spending needs to be increased, but resources from corporations and individuals should also be mobilized. Since China's economic reform in 1979, national healthcare spending has increased from 11 billion yuan in 1978 to 984.3 in 2006.[32]

Putting reform into practice, the roles of preventive healthcare and community health services are increasingly recognized by China's health authority. From 2003 to 2008, community health services were further developed to cover 93–98% of city areas and 50% of town areas. By 2008, approximately 24 000 community health service units had been set up in city and town areas. Meanwhile, there was an emphasis on improving healthcare services in rural areas, which included programmes to improve the training of local health professionals as well as attracting doctors from city areas to serve in rural areas.[24]

Regarding long-term care for the elderly population, nursing home care is an inevitable care model for frail older persons in China. Currently, approximately 1.5% of the elderly population live in nursing homes and apartments for older people.[34] As mentioned above, the one-child policy has resulted in a rapid decrease in family size in China, and a decline in the family support tradition for older family members is expected in the coming years. Hence, the demand for nursing home care will continue to increase,

particularly in big cities. For example, Beijing city added 15 000 nursing home beds in 2010 – an increase of 43%![32]

Geriatric medicine in China and Hong Kong SAR

Geriatric medicine has been defined as a branch of general medicine which deals with the clinical, rehabilitative, psychosocial and preventive aspects of illness in elderly people. Despite an emphasis on the impact of the ageing population, geriatric medicine has not yet been developed in China. Traditionally, there is a group of doctors who practice 'geriatrics'. They are responsible for the delivery of medical care to 'elderly' and senior government officials in China. With the increasing number of retired senior government officials, the demand for their clinical services has also increased. Most of these doctors are well trained and specialized in one particular organ-based discipline (e.g. cardiology, respiratory medicine, neurology). Their training and clinical practice in 'geriatrics' are different from geriatricians in other parts of the world. Their research works are primarily targeted at an organ-based approach which includes cardiac diseases in the elderly, dementia, osteoporosis, biological mechanisms of ageing and anti-ageing drugs. However, there is a lack of research in geriatric syndromes such as falls or clinical models of geriatric care.

Medical education and training programmes in geriatric medicine and gerontology

As the elderly population increases, professional care in geriatric medicine and gerontology has an important role to play. There is a great need to provide education and training programmes in this area for doctors, nurses, social workers and allied health professionals. The current provision is grossly inadequate in China. There is only one undergraduate educational programme on social gerontology at the tertiary education level at the People's University of China, which was started in 1994.[4]

Basic undergraduate medical training in Chinese medical schools includes both a general and a shorter special diploma curriculum. The duration of the general comprehensive curriculum is usually 5 years, but may be 6–7 years in some schools. In terms of scope, this is comparable to primary medical training in other countries. In 1999, there were 21 university-based medical schools and 69 independent medical schools.[35]

High-school graduates may also study the special diploma programmes, which usually take four years. These medical training programmes are not comprehensive and each focuses on one special area only (e.g. oral health, hygiene, child health, physiology, pharmacology, chemistry, clinical medicine, physics, basic medical sciences, Chinese medicine, preventive medicine, medical imaging, acupuncture, etc.). In 1999, there were 20 medical diploma schools and 15 colleges with medical diploma courses.[35]

Geriatric medicine educational programmes in mainland China

Geriatric medicine education is lacking in most medical schools. In the undergraduate medical training in China, teaching of geriatric medicine is included in the curriculum of only 2.9% of medical schools. Most doctors in China are not equipped with knowledge in this area when they graduate from medical schools. This policy is not in keeping with the needs of an ageing population in mainland China and is different from many parts of the world. In Hong Kong SAR, United Kingdom, Europe and other developed countries, geriatric medicine is included in the core teaching of the undergraduate medical curriculum. In the United States, 60% of medical schools have included geriatric medicine as either a core or compulsory module, while 40% include this as an optional module.[35]

In mainland China, there are as yet no formal clinical post-graduate educational programmes for doctors or allied health professionals in geriatric medicine. This indicates that although China has paid great attention to family planning and population control, the university education system has not adapted to the needs of an ageing society. Compared to the widespread availability of post-graduate medical training in geriatric medicine in countries such as the United Kingdom, United States, Canada, Europe, Hong Kong, Australia and New Zealand, it is clear that this lack should be rectified.[6,10,11,35–37]

Specialty status for doctors in China primarily follows their research degrees (e.g. Master's and PhD degrees) as well as their publications in those specialty areas (e.g. geriatric cardiology, osteoporosis, basic science in ageing mechanism, dementia). There is no formal clinical specialist training for physicians in a subspecialty (e.g. cardiology, neurology, or geriatric medicine). Thus, most professors in current geriatric departments usually have a research interest in diseases that are prevalent in old age.[38,39]

The Chinese Geriatrics Society has been publishing the *Chinese Journal of Geriatrics* since 1982. The papers published can be categorized into disease-based research findings, biological mechanisms of ageing and anti-ageing interventions. There is a lack of publications on clinical geriatrics services, geriatric assessment, models of geriatric care and inter-disciplinary interventions. The summary report of the Fourth Committee meeting of the Chinese Geriatrics Society of the Chinese Medical Association emphasizes mainly research works on ageing, anti-ageing, anti-ageing drugs, longevity, geriatric cardiology, geriatric respiratory diseases, dementia and molecular biology, etc. The report also describes future problems which include epidemiology

research in diseases in the elderly, basic scientific research, clinical research on common geriatric diseases and health promotion.[40] Unfortunately, the problems of the lack of clinical services in geriatric medicine and the need to train specialists have not yet been fully appreciated. The current trend of continued development of pure organ-based specialists to look after frail geriatric patients who have multiple problems is detrimental to the quality of care and the healthcare cost for most geriatric patients. This will perpetuate fragmentation of care, neglect of atypical presentations of diseases in the elderly, unnecessary investigations, iatrogenesis related to the duplication of drugs and potential interactions related to multiple medical care providers.

Clinical service in geriatric medicine

Geriatrics departments have existed in China for a long time. The traditional role of doctors in these departments is to provide hospital care for senior government officials (working or retired). The range of specialty skills in this group of doctors may range from neurologist, cardiologist, intensive care physicians, urologist, and so on. The focus is still on organ-based hospital specialists. This is very different from the practice of geriatric medicine in other parts of the world.[36,41–45] See also Chapters 143–145 on systems of healthcare in the United States, Australia and the United Kingdom. The principles of geriatric assessment and interdisciplinary intervention are not practiced. Geriatric rehabilitation is also not available in the clinical service programmes of these departments.

The health and long-term care system for the elderly in Hong Kong SAR

All Hong Kong citizens are entitled to inexpensive health and social care services. Moreover, for those who are on the Comprehensive Social Security Allowance (CSSA) Scheme, service fees are waived. The latter scenario is common among frail elderly patients in public hospitals. Together with escalating healthcare costs and an ageing demography, the annual budget of the Hong Kong Hospital Authority has increased by 19% from HK$27 801 million in 2004/2005 to HK$33 041 million in 2009/2010. With this magnitude of funding increase, the Hong Kong Hospital Authority has no deficit currently.[46,47]

The Social Welfare Department has been responsible for policy and funding of social services up to now. At present, social services for the elderly are categorized into community support (non-residential) and residential care services.[48] In the past, long-term care services for the elderly referred primarily to residential care services, which are largely provided by non-government organizations (NGOs). Over the past decade, the private old people's home industry has been developing rapidly and private homes now form the main service group for residential care of the elderly in Hong Kong. Meals delivery and personal care services are the key non-residential home care services available to those living in their own homes. The great demand for long-term residential care services has been a problem for many years and the magnitude of this problem is on the increase. At present, institutional care is quite commonly utilized and approximately 8% of the elderly in Hong Kong now reside in residential care homes for the elderly (RCHEs) and the hospital infirmary.[14,48–50] The majority of the RCHEs in Hong Kong are low-quality private homes, and a minority are government-funded and self-financing.

History of the development of geriatric medicine in Hong Kong SAR

On the basis of the British model, Hong Kong established its first geriatric unit in 1975. In the initial 10 years, development of geriatric medicine was slow. However, in recent years, the importance of geriatric service to the elderly community has been gradually recognized. At present, there is at least one geriatric service per hospital cluster (Tables 146.7 and 146.8).[14]

Lack of a systematic approach in acute geriatrics care in Hong Kong SAR

A fundamental and serious problem in the present organization of hospital care for the elderly is the lack of a systematic approach to acute geriatrics care. While a multidisciplinary, multidimensional geriatric assessment is frequently practiced in extended care hospitals, there is a general lack of an acute geriatrics service in most acute care hospitals. At present, only 3 out of 15 acute hospitals have designated acute geriatric wards (Table 146.7).[14]

The number of elderly in acute care hospitals is a huge case load. To be cost-effective, acute care for the elderly has to be focused. To attain a cost-effective healthcare model, targeting of the frail elderly patients in the acute geriatrics care programmes is necessary. These targeted patients would be physically, cognitively, and/or psychosocially frail. The settings of screening geriatric assessment would be at the sites where the frail elderly are present (i.e. medical, surgical, orthopaedic and emergency room settings). Concurrent with acute treatment of the presenting medical disease, geriatric assessment and intervention should be started simultaneously to prevent and reverse functional decline.

The unit for development of acute care for the elderly should include several core elements in its programme: targeting of frail elders (i.e. in the emergency department, general medical, orthopaedic, neurosurgical and surgical wards with particular attention to those elderly who

Table 146.7 Geriatric service in the Hong Kong Hospital Authority by hospital clusters.

Year	Cluster	Hospital	Unit/Ward/Team
1994	Hong Kong (HK) West	Queen Mary Hospital (QMH)	Geriatric Team
1994		Fung Yiu King Hospital (FYKH)	Geriatric Department
2002		Tung Wah Hospital (TWH)	Geriatric Team
2004		Grantham Hospital (GH)	Geriatric Department
1990	Hong Kong (HK) East	Rutonjee and Tang Siu Kin Hospitals (RTSKH)	Geriatric Department
1995		Pamela Youde Nethersole Hospital (PYNEH)	Geriatric Team
1996		Tung Wah East Hospital (TWEH)	Geriatric Team
1995		Wong Chuk Hang Hospital (WCHH)	Geriatric Department
1995		Saint John Hospital (SJH)	Geriatric Department
1996		Cheshire Home Chung Hom Kok (CCH)	Geriatric Team
1974	Kowloon East	United Christian Hospital (UCH)	Geriatric Ward
2000		Tseung Kwan O Hospital (TKOH)	Geriatric Team
1991		Haven of Hope Hospital (HOHH)	Geriatric and Rehabilitation Unit
1975	Kowloon West	Princess Margaret Hospital (PMH)	First formal Geriatric Department
1978		Caritas Medical Centre (CMC)	Geriatric Department
1982		Kwong Wah Hospital (KWH)	Geriatric Unit
1994		Yan Chai Hospital (YCH)	Geriatric Team
1995		Our Lady of Maryknoll Hospital (OLMH)	Geriatric Team
1995		Wong Tai Sin Hospital (WTSH)	Geriatric Team
1993	Kowloon Central	Queen Elizabeth Hospital (QEH)	Geriatric Team
1995		Kowloon Hospital (KH)	Geriatric and Rehabilitation Unit
2003		Buddhist Hospital (BH)	Geriatric Team
1985	New territories (NT) East	Prince of Wales Hospital (PWH)	Geriatric Team
2001		Shatin Hospital (SH)	Geriatric Unit
1997		Alice Ho Miu Ling Nethersole Hospital (AHMLNH)	Geriatric Team
1998		Tai Po Hospital (TPH)	Geriatric Team
1990	New Territories (NT) West	Tuen Mun Hospital (TMH)	Geriatric Department

are residents from old people's homes), comprehensive geriatric assessment, case-based conference by interdisciplinary team, and intervention. The interdisciplinary management should include a 'Prehab' programme to prevent functional decline with an appropriately designed acute care ward environment and then a 'Rehab' programme to reverse functional decline and improve activity of daily living. Discharge planning (i.e. predischarge planning and postdischarge support with appropriate placement) with a case management approach should be implemented. Clinical outcomes must be optimized while unnecessary hospital admissions prevented.[36,51]

Inadequate rehabilitation after acute illness is also a problem and the waiting time for Geriatric Day Hospital (GDH) is long. Inadequate GDH transportation is another obstacle to providing adequate day rehabilitation for the frail elderly. Because of moderate disability, they usually require transportation support (e.g. Non-emergency Ambulance Transport) from home to the GDH.[14]

Issues in primary healthcare for the elderly in Hong Kong SAR

For the general population, primary healthcare is largely provided by the private healthcare sector, and the government is responsible for approximately 10% of this service. The latter is provided by the general outpatient clinic. In the elderly, the proportion of private doctor consultation is less than in the young and approximately 70% of them consult general outpatient clinics for primary healthcare problems.[52] Most of the patients attending these clinics are either old or financially poor. Primary care providers are mostly private doctors who can manage episodic health problems well, but are inexperienced in detecting and managing chronic geriatric problems and syndromes. For

Table 146.8 Geriatric services in the Hong Kong West Hospital Cluster.

Acute hospital care	QMH (Integrated model)
	GH (Direct transfer from Emergency Room)
Convalescent care	FYKH
	TWH
	GH
Geriatric rehabilitation beds	FYKH
	TWH
	GH
Long-stay infirmary beds for geriatric patients	FYKH
	TWH
Pre-discharge programme and post-discharge support	QMH, TWH, FYKH,GH
Geriatric Day Hospital as day rehabilitation centre	FYKH
	TWH
Geriatric Specialist Clinics	QMH Geriatric Specialist Out-Patient Department
	QMH Memory Clinic
	QMH Falls Clinic
	QMH Nutrition Clinic
	FYKH Continence Clinic
Hong Kong West (HKW) Community Geriatric Assessment Team (CGAT)	Outreach Geriatric Doctor Clinics in >60 years old people's homes (Subsidized Care & Attention homes, private old people's homes, day care centres)
	Visiting Medical Officer (VMO) under CGAT-VMO programme
	Central Infirmary Waiting List (CIWL) clients pre-admission assessment
	Domiciliary visits: medical, nursing, physiotherapy and occupational therapy
	Educational and training programme for carers and community elders
	Health education programmes with community partners

Note: For hospital name abbreviations, please refer to Table 146.7.

example, dementia is sometimes referred to as a 'normal ageing phenomenon' without appropriate investigation and treatment.

Health promotion to improve lifestyles (e.g. quit smoking, healthy diet, exercise, etc.), disease prevention (e.g. falls prevention and influenza vaccination for the elderly), and early chronic disease identification and control are important. These measures would improve the health of the whole population and decrease geriatric health problems and the need for long-term care in the years to come. Seasonal influenza vaccinations for the elderly with chronic diseases can decrease the chance of influenza-related complications as well as reducing the rate of hospitalizations.[53]

The Department of Health's Elderly Health Service (EHS) provides a health promotion programme for elderly members at their centres.[54] However, data regarding improvement of the health status of elderly participants in these programmes have not yet been reported. Moreover, elderly citizens who are not members of these centres do not have access to the programmes.

Geriatric healthcare at residential care homes for the elderly (RCHES) in Hong Kong SAR

Those elderly living at home and alone constitute 12.4% of the over 65 year olds (11.2 and 13.6% for elderly men and women respectively).[55] While community and primary healthcare is largely provided by private family doctors and general outpatient clinic (GOPC) doctors, specialist geriatric services at old people's homes are provided mainly by a Community Geriatric Assessment Team (CGAT) and partly by Community Health Nurses (CNS).[56,57] A new programme of Visiting Medical Officers (VMOs) was started in October 2003 to improve areas of infection control and provide ad hoc primary or geriatric medical care for frail elders in old people's homes. Approximately 100 VMOs have been appointed as part-time HA staff to upgrade the previously inadequate primary and geriatric care in over 100 old people's homes in Hong Kong.[46,58] The success of this VMO programme has led to its implementation throughout Hong Kong. Recent evaluations also showed that the VMO programme has reduced the number of emergency hospital admissions from old people's homes and hospitalization-related healthcare costs.[59,60]

Service gap and duplication issues for health and long-term care of the elderly

Multiple and continuous gaps in our traditional care models may lead to the 'falling through the cracks' phenomenon.[61] The fragmentation of care can lead to frustration of the elders and caregivers and cause potential harm to patients, for example, being subjected to either 'multiple repeated or similar drugs' (multiple doctors) or 'no drugs' (waiting for new case appointment). The latter is a common transitional care problem for the elderly in Hong Kong.

In the community, the single frail elder commonly receives multiple healthcare services (e.g. the private family doctor, VMO, orthopaedic doctor, ophthalmologist, cardiologist, endocrinologist, etc.) as well as multiple social services (e.g. members of several multiservice or social centres for the elderly, home help services, etc.). The current problems include fragmentation of care, service gaps, overlapping of services, poor communication and coordination. It is believed that an integrated geriatric

health and long-term care team across both health and social sectors would be able to overcome these undesirable issues substantially.

Unfortunately, the current financing and public policy do not facilitate this development. Moreover, the present public health and social policy still lead to unhealthy competition for clients as well as creating some important gaps in services for the elderly. At present, separate service providers are under different budget holders in the Department of Health's Elderly Health Service (EHS of DH), Hospital Authority (HA), Social Welfare Department (SWD) and NGOs. Most elders use the public health and social long-term care services. Only a small proportion of the elderly population seeks services from private hospitals, clinics and social services. In general, the objectives and policies of different service organizations differ. The policy on service directions may also be different. In terms of collaboration between different elderly service providers, a service purchase model among different organizations is in operation, but this has great limitations on breaking the gaps or eliminating service overlaps. For example, frontline staff have difficulty in working together as an integrated team despite overlapping of services (e.g. EHS of DH and Geriatric Service of HA). Loose collaboration is the practice at present, which is not ideal.

For the interface issue between public and private health sectors, there is a slow development. Communications have improved and private doctors can obtain a discharge summary of their patients from HA if they have preregistered. The recent public–private collaboration with VMOs in the Caritas Evergreen Home is one of the successful pilot projects implemented by the author in the Hong Kong West (HKW) Hospital Cluster.[58]

The present organization of healthcare for the elderly indirectly gives rise to an overuse of hospital care services as against community care services. The trend for cost containment would shift hospital care from acute to subacute hospital care, and shorten the length of hospital stay in the acute care hospital per episode of admission. This is a consequence of concentrating only on the activity figures. There is no cost incentive to decrease unnecessary hospital readmissions. Moreover, there has been an overemphasis on specialty-led and organ-based disciplines, which are all very costly.

Thus, alternative health and long-term-care service models for the elderly with an appropriate healthcare financing policy are needed urgently. Effective solutions should be explored and implemented in the near future to avoid catastrophic incidents in both health and social care services for the elderly.

Financing of the public healthcare system for the elderly in Hong Kong is inadequate. Most elderly persons in Hong Kong are poor and obviously would choose to use public healthcare services (under Hospital Authority and Department of Health) rather than the private sectors. The financial status of current and next-generation older persons is definitely not good or optimistic. Recently, the Hong Kong SAR Government has implemented a pilot health voucher scheme with a view to reducing the imbalance of public–private healthcare services utilization. Under this scheme, all elderly citizens aged 70 or over are entitled to consult private doctors, who would be reimbursed the consultation fees with a ceiling of HK$500 per year. The scheme was launched on 1 January 2009. By the beginning of December 2009, 40% (0.26 million) of elderly people had enrolled in the scheme, and over 321 000 doctor consultation reimbursements had been processed.[62]

Recommendation for an integrated health and social care delivery system in Hong Kong SAR

A comprehensive long-term and geriatric healthcare programme is needed for the elderly in Hong Kong SAR. This programme can be subdivided into regional teams. The geriatric health and social long-term services must be fully integrated. We need to improve on the present interface and collaboration models further. Financial incentives are crucial for the success of this model. Merging different organizational structures to form an integrated long-term and geriatric care team is a cost-effective and sustainable way of providing targeted care to the frail elderly among the elderly population of Hong Kong.

Conclusions

The population of China is rapidly ageing. Declining birth and mortality rates and 25 years of the one-child policy are the main reasons for this phenomenon, particularly in urban cities like Shanghai, Beijing and Hong Kong SAR. Recently, the Chinese Government has implemented healthcare reforms to improve healthcare coverage and the insurance system, particularly for rural areas. However, the practice of geriatric medicine with an interdisciplinary intervention is the most suitable clinical management approach for frail older persons in China. Unfortunately, this has not yet started in most parts of China except the Hong Kong SAR. To cope with the demands of an ageing population, there is a definite and pressing need to develop clinical geriatric services together with geriatric medicine educational programmes. Research in local clinical geriatrics care models is also essential for a proper evaluation of their effectiveness. In Hong Kong SAR, further improvement in the practice of geriatric care is needed. The fragmentation of health and long-term care services needs to be rectified in the near future. Integration of geriatric services with social long-term care services for the elderly is recommended.

Key points

- The population of China is ageing and the proportion of elderly >60 years is over 10%; in the 2005 population survey, the elderly population aged >65 years was already >100 million.
- Geriatric medicine has not been developed in most parts of China except the Hong Kong SAR.
- Educational programmes in geriatric medicine at undergraduate and graduate levels and clinical training programmes for doctors are greatly needed in most parts of China.
- Clinical geriatric service with an interdisciplinary team approach should be developed in China. Research in these clinical geriatric care models has to be performed simultaneously.
- The issue of inadequate healthcare insurance for older persons in China, particularly those in rural areas, has improved but needs further development. Financial contributions from the government, the older persons and families are needed.
- The basic principle in China's ageing policy is to maintain sustainable development by setting up an elderly support system partnership involving the state, the community, the family and the individual.

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CHAPTER 147

Ageing in developing countries

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Introduction

The number of older people in many developing countries is growing more rapidly than those in industrialized nations. However, population ageing also reveals social inequality. In South Africa it is interesting to note that only 7% of the blacks, people of colour and Indians (who constitute 89% of the total population) are old people, whereas 14.2% of the minority white population are 60 years and over.[1] Other determinants rather than the Gross National Product (GNP) have a strong influence on life expectancy. Cuba, Costa Rica, Barbados and Sri Lanka are low-income countries with life expectancy similar to North America and many industrial countries of Europe.

The usual view of the developing world held by people living in the West, namely that of families with many children and high infant mortality rates, nowadays applies only to the least developed countries, mainly in Africa. Major fertility reductions in the developing world took place over the last three decades of the twentieth century. From 1950–1955 to 2005–2010, the total fertility rate in the developing world dropped by almost 60%, from 6.2 to 2.7 children per woman.[2] In 2009 the fertility rate in Brazil was similar to the rate in France (1.9 children per woman). Children begging in the streets of some Latin America countries for instance, reveal a lack of adequate social policies despite the reduction in fertility.

There are several possible explanations for the recent demographic scene in the developing world; these include urbanization, improvement in basic sanitary conditions and education, better health assistance and economic growth. Dissemination of information and access to the health system, including distribution of oral contraceptive pills, have strongly contributed to the decline in family size. Greater female participation in the labour market has also played a key role. The size of families parents wish to have has declined, as the cost of raising a child has risen and child survival has increased.[3] In China, government intervention consisted of the coercive and unpopular one-child policy.

Demographic development poses widespread social and economic challenges for societies. The total dependency ratio is a measure of potential social support needs. It represents the ratio of children (persons under age 15) and older persons aged 65 and over to the number of potential working people aged 15 to 64, expressed per 100 population. In developing countries there will be a fast shift from young to old age dependency, since the number of children is declining and the proportion of older persons is increasing rapidly. In African countries with a high prevalence of HIV/AIDS the supposed support given by potential working adult people does not always apply. Many older Africans find themselves in a double-bind. They constitute the majority of the community in the rural areas, responsible for the care of their ill and dying relatives. After sick relatives pass way, older people are often left with grandchildren to support with no middle-age generation present. In Africa alone, 12 million orphaned children grow up without their parents and very often live with their grandparents.[1]

One of the key challenges confronting developing countries with an increasingly ageing population is to guarantee to the whole elderly population an adequate level of income, without placing excessive demands on younger generations and national economies. This dilemma has direct implications for social security systems. Many countries do not have a full pension scheme covering all the working population, mainly those in informal activities or living in rural areas. The increasing life expectancy has not been fully considered by social security schemes in many countries, and a move from early retirement would require a major change in sociocultural model attitudes. In developed and developing countries, early withdrawal from the labour market is currently seen as both desirable and acceptable, even for people in full possession of their faculties and in sound health.[4] At the same time in nations with low and middle economies, elderly people who did not make any contribution to social security are left without any income. However, it is estimated that at least 50 developing

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countries provide social pensions for their elderly citizens, defined as non-contributory cash income.

Social security systems will also be stretched in response to the new demands made by the health needs of older persons.

Ageing and health

The epidemiological transition is the correlate of demographic transition in health. Deaths due to communicable disease are declining and there is a worldwide increase in deaths due to chronic disease, mainly cardiovascular disorders, cancer and diabetes. Despite this trend, it is appropriate to consider that developing countries are facing an epidemiological polarization. Communicable disease remains an important cause of morbidity and mortality, notwithstanding the predominance of deaths due to chronic disorders. Increased vulnerability, a hallmark of the poor and the elderly, and inequity make the risk of infectious disease unfairly high, depriving this section of the population of benefits of human progress achieved as long as a century ago.

In 2002, chronic diseases were responsible for 46% of all deaths in developing countries, a figure that is projected to grow to 59% by 2030.[5] However, the increased risk of chronic diseases is not simply a result of a reduction in infectious disease mortality, nor due to an ageing population alone. Life-course epidemiology reminds us of a new approach to chronic disease. Subnutrition and an unhealthy environment in early life may increase the incidence of chronic disease in later life. So, today's epidemiological scene in developing countries may also reflect past conditions of people who survived despite sub- or malnutrition and poor health conditions in early life.[6] There is a significant association between economic status and good, basic and advanced functional ability. Geriatric functional ability is closely associated with income not only in developing countries, but also in developed countries.[7]

Behavioural risks are estimated to account for 30–60% of chronic disease. In developing countries experiencing economical growth without a corresponding increase in the education level, new behaviours can be imposed by poorly controlled publicity inducing the consumption of tobacco, alcoholic beverages and junk foods.

At the same time as the world is shocked by images of starvation in African countries at conflict, the current trend in developing countries toward higher fat, more refined diets that augment the risk of chronic disease is increasing. Obesity is particularly high in Latin America and the Caribbean. On the other hand, a lack of policies to meet the nutrition needs of the elderly is placing the senior population at even greater risk of food insecurity and malnutrition.[8]

Mortality statistics reveal a limited scope of the health pattern of a population. Chronic disease is by definition a long duration disorder that, before causing death, can impact the patient's life in several ways. The Disability Adjusted Life Year or DALY is a health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of 'healthy' life lost by virtue of being in states of poor health or disability. DALYs for a disease or health condition are calculated as the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition. According to the Global Burden of Diseases estimates for 2004, 68% of the 751 million years lived with disability (YLD) worldwide are attributable to chronic non-communicable diseases, and 84% of the burden of chronic disease arises in countries with low and middle incomes.[9] Although the prevalence and incidence of most chronic diseases are strongly age-dependent, only 23% of the disability burden caused by chronic disease in countries with low and middle incomes occurs in people aged 60 years and older, compared with 36% for high-income countries, where demographic ageing in much more advanced.[10] Thus health conditions of old people living in developing countries tend to be worse than those who live in high-income countries, reflecting also adversities in early life, nutrition problems, unhealthy lifestyle and lifelong insufficient healthcare. Differentials in education contribute to prevalence of disability at ages >65 years independently of disease.[11] Thus education remains the most important correlate to health with tough consequences in old age. Whereas the current generation of older adults in much of the developing world is characterized by low and gender-segregated levels of education, offspring have higher levels of education and the gender gap has closed considerably. It may therefore be expected that older adults are exposed by their children to a new set of beliefs and an expanding knowledge base that may alter and expand available resources.[12]

In the next 30 years developing countries will pay for their tormented past even if socioeconomic growth continues. There will be a dramatic shift in the distribution of death from younger to older age and from communicable to non-communicable causes. Most developing countries are not sufficiently equipped to meet the needs of the older population, mainly the leading causes of YLD: eye disease, hearing loss, dementia, musculoskeletal disease and heart disease. Although it is not so difficult to implement healthcare for cataracts and hearing loss, for example, the demands of the three latter disorders are complex and more difficult to attend.

Health care and geriatric medicine

To be elderly in middle- and low-income countries is to have a high chance of being in adverse health conditions. This reveals the challenge that countries with a recent history of

demographic 'shock' will face. Lives are not saved, rather death is postponed. Thus developing countries will have to deal with the expensive and complex demands related to the care of the 'survivors' of the socioeconomic traps imposed by poverty and ignorance, contrasting with the simple and less expensive (per capita) investment made in sanitation, vaccines and the use of antibiotics that allowed children and young adults to survive into old age.

Health systems in less developed countries are not uniform. There are very well-equipped institutions in most countries; however, primary care attention is somewhat deficient. In countries like Cuba where there is comprehensive healthcare, life expectancy is high. In the developing, and also in the developed world, geriatric medicine has a long way to go. In Africa only some northern countries have a few geriatric centres. China, as the country with the greatest elderly population, is reorganizing its public health system. Their Medicare system coverage is not available to two fifths of employees in cities and towns, and even less to workers living in rural areas.[13] It is difficult to assume that a high standard of medical care for those above the age of retirement will soon be available. Many Indian geriatricians have made important contributions to the quality of geriatric care in the United Kingdom, whereas in India, work in geriatric medicine has mostly been an application of the principles of general medicine to disorders and conditions related to old age. Departments of geriatric medicine are just beginning to come into being.[14]

In Latin America the geriatric societies are very active but the incorporation of the principles of geriatric medicine by the public health system is far from satisfactory. Although the health services are under pressure due to the new demands of the older population, there is very little or nothing specifically to meet their needs. The rather poor teaching of geriatric medicine in medical schools has, as a consequence, the under-diagnosis of problems of elderly patients, making the 'iceberg phenomenon' a common condition at the same or at a higher level than it was 50 years ago in the United Kingdom.[15]

It took a long time for health systems to set up assistance to acute problems. Although in many countries this assistance is criticized, a new challenge is on the table: to increase the capacity of health systems in transforming systems from acute to chronic care. In many countries the unsatisfactory response of the public sector has led to the increasing privatization of healthcare. In this context, it must be underlined that elderly individuals when sick, have higher expenses in the face of lower incomes and that the transition from public to private responsibilities carries some risks – the 'cream skimming' of private sectors selecting those younger and wealthier, and thus selective exclusion of women, the less well-off, and the elderly who tend to remain under the public sector's responsibility.[16]

As formal care for geriatric patients has to be improved or even built from scratch, more is expected from informal care, especially that provided by families. However, families in the developing world are far from the romantic model of supposed grandparents being respected for their contribution to society and for their wisdom, who live surrounded by happy grandchildren begging for another story.[17] India is a country with a hoary past, with traditions of family care of the elderly, but this traditional care is in jeopardy of disruptive influences from modernization, migration and dual careers, thus posing a direct challenge to the policy-makers.[1] Most family care in developing countries involves women; so the inclusion of female in the labour sector is another reason for the reduction of traditional care in developing countries.

Population ageing does not always mean reaching 65 years of age. In developing countries a significant proportion of the elderly population is represented by people of 75 years and over. There are more than 10 million people aged 75 years or over in Africa, and almost twice this number in Latin America and the Caribbean. In this age group it is imperative to plan long-term care. The percentage of elderly people living in institutions is as low as 0.1% in Iran, 0.6% in Botswana, nearly 1% in Brazil and Mexico compared to 7.5% in Switzerland. Ironically this lack of infrastructure opens the way to create alternative, community-based long-term care systems.[16] Data indicate there will be a rising need of long-term care even in developing countries in the future. Higher relative percentages of oldest olds with more *activities of daily living* (ADL) impairments, rising costs and fewer sources of informal care will stretch countries' resources to the limits. Economic privatization efforts will only push more of the costs back onto the families, where the greatest burden of care already lies, especially among those caring for the elderly with diseases such as Alzheimer's.[18]

Specific increases in costs and health needs for the population, and the subsequent pressure that will be placed on formal and informal healthcare systems will depend on factors such as incidence and prevalence, rates of health disorders and how these change concurrently with an ageing population.[12] In developing countries the project pressure will be high since the compression of mortality into old age does not necessarily mean that compression of morbidity will also be achieved.

Key points

- There are more than 10 million people aged 75 years or over in Africa, and almost twice this number in Latin America and the Caribbean.
- One of the key challenges confronting developing countries with an increasingly ageing population

is to guarantee to the whole older population an adequate level of income, without placing excessive demands on younger generations and national economies.
- Most developing countries are not sufficiently equipped to meet the needs of the older population, mainly the leading causes of years lost due to disability (YLD): eye disease, hearing loss, dementia, musculoskeletal disease and heart disease.

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CHAPTER 148

Geriatric medicine in the European Union: towards unification of diversity

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Introduction

Europe has a landmass of 9 938 000 km^2, 6.7% of the total land area on earth. Unlike the United States of America, Europe is not a federation of states with a unifying governmental structure, but a continent that groups 49 very diverse countries, with long and diverse history, languages, climates, customs, traditions, cultures, populations and governments. However, in the last century the European Union (EU) has provided a certain amount of integration between the member states in terms of laws, trade and governmental policies. At present, the EU has expanded to 27 member states, and a number of other countries have applied to become members. In 2010, the EU had 499 million inhabitants – the world's third largest population after China and India – and includes many of the countries with the world's highest proportions of older people.

The EU developed after World War II, with the aim of ending the frequent and bloody wars between neighbours, and has been growing in number of countries and depth of understanding ever since. EU citizens have freedom of movement of goods, services, people and money within their countries. Passports are not needed to move within most countries, and many share now a common currency, the Euro. The EU brings many unifying initiatives, but countries have the right not to join many multilateral EU initiatives, which helps to explain the present heterogeneity of the Union. Active debate is ongoing on the need for a European constitution.

The EU is not a traditional federation of countries, neither is it a common organization for cooperation between governments, like the United Nations. Member states of the EU remain independent nations but they delegate some of their decision-making powers to shared institutions, so that decisions on specific matters of joint interest can be made democratically at European level. The EU has a complex structure, where three main institutions participate in decision-making. The *Council of the European Union*, which represents the individual member states, is the main decision-making body, where ministers from each member state can commit their government to various EU policies. The *European Parliament* represents the EU's citizens, its members being elected directly by voters in each state. The *European Commission*, based in Brussels, Belgium, is the civil service of Europe, and is independent of national governments. Its job is to represent and uphold the interests of the EU as a whole. It is split into various directorates which each have an appointed political head combined with an overall Commission President. The Commission has responsibility for proposing European legislation (the Parliament and Council decide on adoption of new laws), implementing agreed policy (together with national governments), enforcing EU law and representing the EU at international level.

Healthcare is not included in the list of common policy areas; only public health is, and this has a critical impact on the provision of healthcare and the organization of healthcare systems around Europe. Each EU country is free to decide on the health policies best suited to national circumstances and traditions, although they all share common values. These include the right of every citizen to the same high standards of health and equity in access to quality healthcare. The EU is also committed to taking into account the implications of health in all its policies and decisions.

Demography

The EU compiles statistics from member states through its agency Eurostat (epp.eurostat.ec.europa.eu), including a great wealth of population- and health-related parameters. However, Eurostat does not collect data directly, but rather collates and tries to harmonize data obtained from national agencies, so problems may arise with the uniformity of their

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collection, not only in terms of completeness but also their comparability and quality. Most relevant statistical data are open access and regularly updated.

Bearing in mind the above, it appears that Europe's population has been ageing steadily for a long time. The total EU population is projected to rise by 5% between 2008 and 2030, and the median age is likely to increase in all but seven out of the 281 European regions, due to the combined effect of three factors: the existing population structure, fertility lower than replacement levels, and steadily rising numbers of people living longer.[1] The proportion of the total population aged 65 or over is projected to increase considerably in the near future, from 17.1% in 2008 (87 million) to 23.5% (123 million) in 2030. The number of very old, aged >80 years, is already 22 million (4.4% of the population), and in 11 of the former EU-15 member states, at least 10% of their population will be aged 80 or over by 2050. Gender differences in ageing are considerable, as life expectancy for women is currently more than six years longer than for men.

These global figures may disguise major variations across the EU countries, both in population growth and in ageing rates. Life expectancy at birth varied in males in 2007 from 64.9 years in Lithuania to 78.9 years in Sweden, and in females from 76.1 years in Romania to 84.4 years in France. The share of the population aged 65 years or over in the 27 EU countries ranged in 2008 between 10.9% in Ireland and 20.1% in Germany (Figure 148.1). Regional variation is even higher, ranging between 9.1% (in Inner London, UK) and 26.8% (in Liguria, Italy). Contrary to expectations, these differences are not diminishing, but are expected to increase in the near future, ranging in 2030 between 10.4% (again in Inner London, UK) and 37.3% (in Chemniz, Germany). The proportion of citizens >80 years in 2008 ranged between 2.7% in Ireland and 5.5% in Italy.

In parallel with these changes, the working population over the same time frame is projected to decrease significantly. The old age dependency ratio, defined as the projected number of persons aged 65 and over expressed as a percentage of the projected number of persons aged between 15 and 64, is projected to increase from 25.9 in 2010 to 38.0 in 2030. This has been called a 'demographic time bomb' and has considerable implications for health and social care planning across the EU.

Major differences between EU member states also exist in active life expectancy (life expectancy with no disability). As

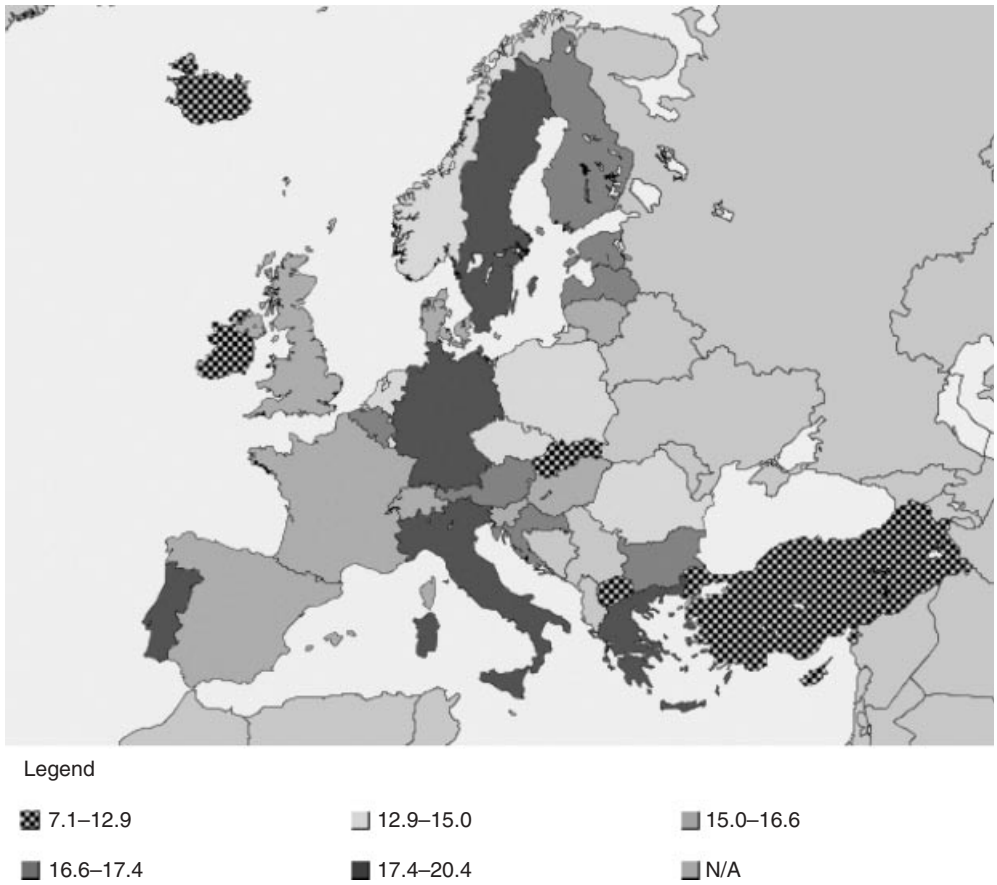

Figure 148.1 Proportion of population aged 65 and over (% of total population). See plate section for a colour version of this image.

a whole, in 2007 men in the EU were expected to live 80.9% of their life without disability, but this ranges from 89.3% in Norway to 71.9% in Germany. Women in the EU could expect to live 75.8% of their lives free of disability, ranging from 87.3% in Malta to 66.2% in Slovakia. Since 2003, the measurement of *Healthy Life Years* is considered a structural indicator on health in the EU, which is a very relevant step forward for geriatric prevention and care planning.

Healthcare and health systems

Medicine has developed in Europe for more than 25 centuries: Hippocrates of Kos (Greece) is considered to be the father of modern medicine, and over the centuries many milestone advances have been made in European countries. There is a centuries-old tradition of medical care, and all the EU member states have systems in place that offer complete, or near complete, rights to healthcare for people residing within their borders. High-quality health services are considered a priority issue for European citizens, and rights to healthcare are recognized in the Charter of Fundamental Rights of the EU. Most countries jealously guard management of their own healthcare systems, so it is no surprise that, with the exception of public health, states retain competence for health policies and health systems, and do not delegate these under EU instances. However, and very recently, health systems policies across the EU countries seem to be more interconnected, due to public expectations, movement of patients and health professionals across countries, and information and medical technology. The EU holds responsibility to complement the work of member states (i.e. in patient mobility or international health threats) and to reduce health inequalities, fostering cooperation between countries.

Healthcare systems in the EU are financed in two broad ways, either through general taxation, or using systems based on social health insurance, although in highly variable proportions. Taxation predominates in some countries (e.g. Denmark, Italy, Spain, Sweden and the United Kingdom), while social health insurance contributions are the predominant source in others (e.g. the Czech Republic, France, Germany and the Netherlands).[2] Both systems usually limit their liability to pay the full cost of treatments, such that expenditure borne by households amounts to 20–30% in the majority of member states. The difference is made up either through direct contributions or via supplementary private insurance. It is, however, clear that public-sector funding makes up a significant proportion of health expenditure in all the EU member states: this proportion being lowest in Greece (56%) and rising to a high 95% in the Netherlands.

Although in most states universal access to healthcare is granted, including for older, impoverished or immigrant populations, the reliance on a degree of financial participation may adversely affect some groups' access to healthcare as they are unable to afford the costs. This is particularly true of older people who may have both lowered incomes and considerable comorbidity. Thus some member states have enacted methods to target older people either by reducing their financial liability or ensuring that they are regularly screened by relevant health professionals. However, the universal access approach is putting a great deal of financial pressure on the sustainability of the whole care system.

The impact of ageing on health and long-term care systems is considered to be one of the most significant challenges for the economies and welfare systems of European countries. According to OECD Health Data 2010, total health expenditure in EU countries in 2008 ranged from 6.1% of gross domestic product in Estonia to 11.2% in France. This contrasts with 16% in the same period in the United States. As most experts predict that increases in healthcare expenditures will continue over the next 50 years, finance is a major issue for most countries. Thus, the economic and financial affairs directorate is carefully examining this currently, estimating and modelling the size and timing of projected changes in expenditure and their underlying driving factors, in order to assess sustainability. Many publications have appeared recently feeding a public policy debate which may force changes in the near future.[3]

Health and ageing trends

Life expectancy has been steadily growing in the EU over the last century, and this trend has not stopped in recent years (Table 148.1). A European citizen aged 65 years may expect to live more than 19 years into 'old age'. This could theoretically mean that diseases and disabilities of old age are steadily increasing, although this is actually challenged.[4] Changes in lifestyles, risk factor management, public health and healthcare have pushed for a slow but steady reduction in some of the main causes of mortality in old people, such as diseases of the circulatory system (a 27.4% reduction in the last 10 years), stroke (32.2% reduction) or cancer (7.8% reduction). However, mental health disorders (particularly dementing diseases and depression) seem to be increasing rapidly during the same time period (an increase of 26.7%), not only in mortality but especially in morbidity.

An enormous variability is also found in the health needs of individual countries within the EU, and differences have increased with the new countries that have recently joined. For instance, the standardized death rate by 100 000 inhabitants for ischaemic heart disease in 2008 ranges from only 33.8 in France to 321.3 in Lithuania, and crude death rates by 100 000 inhabitants from suicide in those aged 85 and over range from 1.9 in Ireland to 64.8 in Hungary in the same year. Thus, health planning in each country

Table 148.1 Health trends in European Union member states in the last 10 years.

	1998	2008	Percent change
Basic demographic indicators			
Population, millions	479.8	496.4	3.5
% of population aged 65+ years	15.33	16.93	10.4
Mortality indicators			
Life expectancy at birth, years	76.84	79.43	3.4
Life expectancy at age 65, in years	17.32	19.06	10.0
Disability-adjusted life expectancy, in years	70.35[a]	71.7[b]	1.9
SDR, diseases of circulatory system, 65+ per 100 000	2437.99	1771.04	−27.4
SDR, ischaemic heart disease, 65+ per 100 000	896.26	638.22	−28.8
SDR, cerebrovascular diseases, 65+ per 100 000	646.54	438.06	−32.2
SDR, suicide and self-inflicted injury, 65+ per 100 000	21.1	17.45	−17.3
SDR, malignant neoplasms, age 65+ per 100 000	1055.71	973.55	−7.8
SDR, mental disorders and diseases of the nervous system and senses	153.31	194.53	26.9
Healthcare resources			
Hospitals per 100 000	2.87	2.62	−8.7
Hospital beds per 100 000	647.61	530.53	−18.1
Acute care hospital beds per 100 000	462.21	378.18	−18.2
Physicians per 100 000	284.91	323.71	13.6
General practitioners per 100 000	82.50	85.59	3.7
Nurses per 100 000	687.96	775.24	12.7
Healthcare utilization and costs			
Average length of stay, all hospitals	10.14	8.72	−14.0
Average length of stay, acute care hospitals only	7.51	6.74[b]	−10.3
Outpatient contacts per person per year	6.69	6.86[b]	2.5
Total health expenditure, % of gross domestic product	7.94	9.01	13.5
Total health expenditure, $ per capita	1661.12	2877.54	73.2

[a] 1999
[b] 2007
SDR: standardized death rate
Source: European Health for All Database, WHO Regional Office for Europe, Copenhagen, Denmark.

needs to take account of these differences, providing health promotion and care systems that are more prone to have an impact on relevant health outcomes in each country.

One of the main problems researchers in geriatric care are faced with when studying illness in older people in the EU is the lack of good morbidity data of geriatric interest. Health statistics are available for communicable diseases, for some chronic diseases, for health habits and lifestyles, and for disease related mortality. However, there are no reliable data regarding geriatric diseases and syndromes (delirium, hip fracture, urinary incontinence), nor in disease related physical and mental disability. Data are fragmented, come from different years and sources, are gathered with different criteria and are not systematically collected. Good age-specific data for older subjects are especially sparse. Research and progress in this area is urgently needed, and several research initiatives funded by the EU are trying to fill this gap.

For instance, research in health and social implications of ageing has been fostered through the *Survey of Health, Ageing and Retirement in Europe* (SHARE, www.share-project.org), a multidisciplinary cross-national database on health, socioeconomic status and social and family networks of individuals over the age of 50. Data collected include health variables (including physical functioning, cognitive functioning, health behaviour and use of healthcare facilities), psychological, economic and social support variables.

Changes in the characteristics of disease in older people are transforming the paradigm of healthcare. Healthcare was developed a long time ago for the care of single, acute diseases, usually unexpected, with cure and self-sufficiency as the usual outcomes. However, older patients usually

have multiple, chronic morbidities (sometimes with acute exacerbations), where disease course can be expected, with dependency as a very frequent outcome. Unfortunately, healthcare systems in Europe, very efficient for acute care, have evolved only slowly and in a very irregular and heterogeneous mode, even within different regions of the same country, to be able to manage chronic diseases in dependent people. This lack of efficiency may explain why per capita health expenditure increases sharply after the age of 65 and even more sharply after the age of 80. Responses to tackle this change of paradigm are still naïve in the EU. Recent moves to promote a comprehensive approach in tackling chronic diseases, including cardiovascular disease, cancer, mental health problems, diabetes mellitus, chronic respiratory disease and musculoskeletal conditions, are still organ-based rather than individual-centred.

Over the last three decades, the number of hospitals and hospital beds has been diminishing, including those used for acute care, while the number of general practitioners, nurses and primary care units has not grown at the same rate. Intermediate and long-term hospital beds have suffered a slower reduction, and rehabilitation and palliative care services for older people are scarce and irregularly distributed, not only between countries, but within different areas of the same country.

In common with other developed countries the member states see the need to recruit staff appropriately trained in the needs of older people and also to create post-acute rehabilitation facilities and other healthcare settings to assist a multidisciplinary approach to treatment with the goal of re-ablement and settlement in the community.[5] Unfortunately, often these rehabilitation sites are adrift from main acute centres in the mistaken belief that rehabilitation can wait till the conclusion of an acute episode of care.

Long-term care has been seen for a long time as mainly a social risk. Recently, it has been acknowledged that long-term care is inadequate in many EU countries and suffers from labour shortages and low quality. Long-term care depends on national governments, so the EU has started a new programme that promotes the coordination of national long-term care policies with a particular focus on universal and equal access to different long-term care services, quality and sustainability, as spending on long-term care is expected to grow fast in view of population ageing.[6] Long-term care services are now judged to be crucial to the welfare of older people, and the importance of these services in terms of numbers of clients and expenditures is expected to grow. Steps to ensure the long-term sustainability of public financing are now being discussed.

Public health, depending on the EU institutions, seems to be focusing more on other ages and groups, not on older citizens. Only a couple of initiatives, including a growing emphasis on nutrition and age, and the promotion of healthy ageing by the development of an integrated holistic approach to health in later life, seem to be gaining momentum in recent years. The debate on the redefinition of the age of retirement, forced by the economic crisis, has provoked an unprecedented public debate on some age-related issues.

Geriatric medicine

Geriatric medical care, as may be expected is also extremely diverse within the EU.[7,8] Geriatric Medicine is recognized in many European countries, either as a lone standing speciality or as a subspecialty of Internal Medicine.[9] It is an official specialty accepted by the EU, but it is not yet available in every country: only 18 of the 27 countries had, in 2006, established the mechanism for mutual recognition of the speciality (Table 148.2), which requires a minimum length of training of four years. However, this list may not present a fair picture of Geriatric Medicine in Europe. In some countries (Belgium, Germany) this discipline has a wide distribution, with academic hospital departments and specific geriatric training programmes, even when mutual recognition has not been achieved. In other countries, even when formally present, Geriatric Medicine is very poorly developed. European geriatricians are working hard to promote recognition of the specialty and development of geriatric medicine departments in every EU country. This comes not without its problems.[9]

It might be expected that a medical speciality department would be somehow similar around Europe, so similar up-to-date procedures will be applied to any patient admitted to a medical department of a hospital, i.e. Cardiology or Gastroenterology. However, this is not completely true for Geriatric Medicine,[10] although very little systematic data exist. Excellent geriatric departments exist in most EU countries, but citizens living in different places will have different access rights to these departments, and a significant proportion of older people in the EU will not have access to geriatric medicine. This is not due to lack of evidence, as very solid evidence exists about the benefits of most levels of geriatric care, but to discrimination against old people by political decision-makers.[5] Primary care is almost universally available for the older population in the EU, but many general practitioners are not prepared to manage this special population due to a lack of academic leaders and continuing professional development in geriatric medicine.

Education in geriatric medicine in Europe is also extremely variable, both at undergraduate and postgraduate level, although it seems to be improving. In a recent survey, only six European countries had an established Chair of Geriatric Medicine in each of their medical schools.[11] Undergraduate teaching activities were not present in many countries and had a highly variable number of hours, and all levels of geriatric teaching were

Table 148.2 Mutual recognition of Geriatric Medicine in the European Union.

Country	Name of discipline
Belgique/België/ Belgien	
България	Гериатрична медицина
česká republika	Geriatrie
Danmark	Geriatri eller alderdommens sygdomme
Deutschland	
Eesti	
Ελλάς	
España	Geriatría
France	
Ireland	Geriatric medicine
Italia	Geriatria
Κύπρος	Πηριατρική
Latvija	
Lietuva	Geriatrija
Luxembourg	Gériatrie
Magyarország	Geriátria
Malta	Gerjatrija
Nederland	Klinische geriatrie
Österreich	
Polska	Geriatria
Portugal	
România	Geriatrie şi gerontologie
Slovenija	
Slovensko	Geriatria
Suomi/Finland	Geriatria/geriatri
Sverige	Geriatrik
United Kingdom	Geriatrics

Source: Council Directive 2006/100/EC of 20 November 2006 adapting certain Directives in the field of freedom of movement of persons, by reason of the accession of Bulgaria and Romania. *Official Journal of the European Union*, 20.12.2006.

heterogeneously organized from country to country and within each country.

Traditionally, family members have accepted a high degree of responsibility in the care of older people in most of Europe, especially the Mediterranean countries. This is changing, with the growing numbers of older people and a reduced ability of weaker family networks to care for them, when they depend on others. This is helping to increase the need for long-term care in different settings (home care, long-stay units or nursing homes). Such care has not been regularly covered by health systems, and it is not a universal right within the EU, in contradistinction to acute healthcare. In many cases it depends on private systems, although some countries are now trying to regulate by law the care of dependent citizens. Nursing home use and availability is also diverse across the EU: rates are close to 10% of people 65 or older in some northern countries (Sweden, Holland) and lower than 3% in some Mediterranean countries (Spain, Portugal), with a gradient from north to south that is not only explained by economic reasons, but depends more on people preferences and family networks.

A last area of concern in geriatric care is the lack of solid research in medicines used by older people. The European Medicines Agency recently acknowledged this was a problem, especially in the very old and frail, and is now actively discussing, under the lead of several scientific organizations, changes that need to be made in the approval process of medicines for older persons.[12]

Geriatric organizations

Europe has a very long tradition of national geriatric societies: for instance, the British Geriatrics Society (BGS) was founded in 1947, the Spanish Geriatric and Gerontology Society (SEGG) in 1948, and the Italian Geriatric and Gerontology Society (SIGG) in 1950. The first World Congress of Gerontology took place in Liège (Belgium) in July 1950, and the *International Association of Gerontology and Geriatrics* (IAGG) was founded at that congress, under the lead of Professor Lucien Brull. The European Region section of the IAGG (www.iagg-er.org) is an umbrella organization of national societies, with a multidisciplinary approach and an aim to foster research, education and cooperation in all branches of Gerontology.[13]

The need to improve specific aspects of geriatric medicine led in 2001 to the creation of the European Union Geriatric Medicine Society (EUGMS, www.eugms.org), a blossoming medical society that is now very active in fostering the development of geriatric medicine in all the member states of the EU, trying to achieve availability of these services to all citizens of the EU, promoting education with very successful annual scientific meetings, and developing documents and guidelines.[14]

The official instance for representations of geriatricians before the European authorities is the Geriatric Section of the European Union of Medical Specialists (UEMS, www.uemsgeriatricmedicine.org). This organization has been able to provide a consensus definition of Geriatric Medicine, documents on accreditation for specialist training and undergraduate training, and is part of the European Accreditation Council for Continuing Medical Education.

The need to raise the level of academic geriatric medicine and to promote leadership both in teaching and research led in 1995 to the creation of the European Academy for Medicine of Ageing (EAMA, www.eama.eu), an organization that is being extremely successful in fostering leading geriatricians.[15] The model of this institution has been exported to Asia and South America.

Recent developments in EU policy

Public health policy and the promotion of a high level of human health is a relevant part of the EU Treaty. Recent developments in the care of older people have been fostered by the European social policy agenda. In March 2000, the European Council in Lisbon set out a ten-year strategy (the Lisbon Strategy), a commitment to bring about economic, social and environmental renewal in the EU to make the EU the world's most dynamic and competitive economy. Under this strategy, social policies that ensure sustainable development and social inclusion were to be fostered, together with improved coordination of teaching and research looking for a knowledge-based society. These policies were based, in many cases, on an improved cooperation between member states, respecting the principle of subsidiarity. However, a mid-term look at the Lisbon strategy found that the outcomes were disappointing.[16]

Healthcare of older people was not seriously considered at the European level until 2001, when the Goteborg Council asked for an initial report on orientations in the field of healthcare and care for the elderly, in conformity with the open method of coordination (a method used to improve coordination in some policy areas, allowing member states to challenge common problems, defining their own national strategies and benefiting from experiences of other member states). This request resulted in a report that carefully analysed the impact of demographic ageing on healthcare systems; expenditure; the growth of new technologies and treatments; an improved wellbeing and a better standard of living; the diversity of national systems and the contribution of the EU. Access to healthcare is considered a fundamental right and an essential element of human dignity that must therefore be guaranteed for all EU citizens, regardless of income or wealth. The need for special protection is recognized for dependency and old age, and the need to improve quality to reduce diversity and variation is also underlined. Financial viability is needed to sustain health and social systems of care in the future. This request finished with a resolution of the European Parliament on the future of health and social care of older people, calling for improvements in accessibility, quality and financial viability.

Later, in 2004, the European Commission issued a new report that sought to outline a common framework to support member states in the reform and development of healthcare and long-term care using the open method of coordination. This report proposed common objectives for healthcare provision that would add to similar ongoing coordinating processes in three social policy areas: pensions, social inclusion and employment. The most relevant aspects of this document related to Geriatric Medicine are outlined in Table 148.3.

These steps by the European Commission are a promising move for geriatric care. Nevertheless, it must be remembered that the Commission can only suggest action lines, which have to be agreed and implemented by member states, and this seems not to be happening at the expected

Table 148.3 Recent European Union action lines related to geriatric medicine.*

- Health systems have a role in combating the risk of poverty and disease, contributing to social cohesion and fighting the consequences of demographic ageing.
- The principles of accessibility of care for all (taking into account the needs and difficulties of the most disadvantaged groups and individuals), high-quality care for the population (which keeps up with the emerging needs associated with ageing) long-term financial sustainability of this care have to be met.
- The provision and funding of health and long-term care are key elements of the economic and social modernization strategy of the EU.
- To meet the challenges posed by demographic trends and technological progress, it is vital to have a sufficient number of trained professionals and to give them quality jobs.
- Demographic ageing will mean more age-related illnesses and more people in long-term care; and a growing number of old people living alone. The response to the needs of this population group will include developing a wide range of services, including care at home, and specialized institutions, as well as closer coordination between care providers.
- The social protection systems need to be reformed in an integrated and coordinated way to meet these challenges. Health and elderly care is one of the areas where coordination in the field of social protection should be streamlined.
- Access to high-quality care based on the principles of universal access, fairness and solidarity must be ensured, providing a safety net against poverty or social exclusion associated with ill health, accident, disability or old age, for both the beneficiaries of care and their families. Particular attention will have to be paid to persons requiring long-term or expensive care, to those with particular difficulties accessing care and those on low incomes. Financial and physical accessibility of care systems for disabled persons has to be ensured, and specific care for elderly people offered, based in particular on closer coordination between the social services, primary carers, hospital services and specialized institutions.
- The system should be properly funded, in order to meet the new challenges posed by ageing, changes in society and technological progress. Responsibility for the organization and funding of the healthcare and elderly care sector rests primarily with the member states.

*Extracted from *Modernising social protection for the development of high-quality, accessible and sustainable health care and long-term care: support for the national strategies using the 'open method of coordination'*. EU COM 304 final, April 2004.

rates. European and national organizations of geriatric medicine specialists have a long way to go to ensure that their older patients have the best multidisciplinary care in the most optimal setting.[5]

European countries are facing a rising demand for health and social services as a result of an ageing population and higher income levels, although the funding available remains limited. At the same time, citizens have higher expectations and the mobility of patients and of health professionals has increased. One of the ways the EU is using to tackle this situation is the development of e-Health systems and services, trying to reduce costs, improve productivity, reducing medical error, cutting down on unnecessary care, and improving the quality of healthcare. These measures may have an impact on geriatric care.[17] Today at least four out of five European doctors have an Internet connection, and a quarter of Europeans use the Internet to get information about diseases and health matters. These encouraging figures indicate that e-Health systems and services will develop rapidly. Estimates suggest that by 2010 up to 5% of health budgets are being invested in e-Health systems and services.

Finally, an important issue that is now actively being pursued is the reform of universities. Despite reasonably good teaching quality, European universities are not using their full potential, and investment in higher education is insufficient. Europe must strengthen education, research and innovation, and universities are essential in these three aspects, so there is a need to invest more, modernize and improve the quality of universities as a direct investment in the future of Europeans.[18] Here, Geriatric Medicine can find its way into teaching geriatric principles to all health professionals, not only to physicians.

Key points

- European countries are facing a rising demand for health and social services as a result of an ageing population and higher income levels, although the funding available remains limited.
- The European Commission is trying, through the open method of coordination, and with the support of many European institutions, to improve access to healthcare, quality of care, and financial sustainability of health and social care systems.
- One of the main problems facing researchers in geriatric care when studying illness in older people in the EU is the lack of good morbidity data of geriatric interest.
- Education in geriatric medicine in Europe is extremely variable, both at the undergraduate and postgraduate level, although it seems to be improving.

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APPENDIX

Function assessment scales

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Components of the geriatric assessment

Dimension	Screening test	Assessment tests
Advanced directives	Do you have an advanced directive or living will?	Detailed discussion Document desires in chart Discuss ventilation separately from cardiac resuscitation Discuss feeding tube Discuss long-term beliefs if the person becomes cognitively impaired Assess the person's ability to make appropriate decisions
Affective	Are you sad?	Geriatric Depression Scale
Alcohol abuse	Do you drink alcohol?	CAGE Michigan Alcohol Screening Test – 9
Blood pressure	In older persons all blood pressures need to be measured at a minimum of sitting and standing	Check for postural hypotension at one and 3 minutes after standing If the person falls, is dizzy, syncopal or has a stroke or myocardial infarction within 2 hours of a meal, check for postprandial hypotension Both orthostatis and postprandial hypotension are more common in the morning Because of arteriosclerotic occlusion of vessels older persons often have a higher blood pressure in one arm than the other. Always treat the higher blood pressure Arteriosclerosis can lead to pseudohypotension. This can be screened for by the Osler Manoeuvre but as it has poor sensitivity and specifically intra-arterial blood pressure may need to be obtained 'White-coat' hypertension is common so always obtain home blood pressures A wide pulse pressure has a poor prognosis in older persons
Caregiver burden	Is the caregiver having problems coping?	Geriatric Depression Scale Caregiver Burden Inventory, looks at time, developmental needs, social burden and emotional burden
Dehydration	How much fluid do you drink each day?	Check serum osmolality Remember elevated BUN to creatinine ratio occurs with renal failure, liver disease, heart failure and gastrointestinal bleeding

(*continued overleaf*)

Principles and Practice of Geriatric Medicine, Fifth Edition. Edited by Alan J. Sinclair, John E. Morley and Bruno Vellas.

Dimension	Screening test	Assessment tests
Delirium	Is the person confused? Does the level of confusion fluctuate?	Confusion Assessment methodology (acute onset, fluctuates, lack of attention, disorganized thinking including illusions, delusions and hallucinations; hyperalert or lethargic)
Dental	Do you have false teeth? Do you have sores in your mouth or gum disease? Do you often have bad breath?	DENTAL screening tool
Dizziness	Do you get dizzy or does your head spin around?	Check for postural hypotension Hallpike Manoeuvre for Benign Paroxysmal Positional Vertigo (BPPV) Haemoglobin Geriatric Depression Scale
Driving assessment	Do you drive? How do you meet your transportation needs?	If poor vision, cognition or motor function refer to a Driving Rehabilitation Specialist to test in either a driving simulator or on-road driving test. This may include monitoring driving when alone utilizing a GPS device. If this is refused. the physician needs to report the patient to the Department of Motor Vehicles as unsafe to drive
Economic	Do you have enough money to pay your bills and purchase medicines and food?	Health Insurance Medicare Part D Can a cheaper drug replace a more expensive one?
Fatigue	Are you easily exhausted (tired)?	Bioavailable testosterone (in males) C-reactive protein, haemoglobin, TSH and vitamin B_{12} Epworth Sleep Inventory for sleep apnoea Fried Frailty Test (see Chapter 113, Frailty)
Function	Do you need help at home?	Barthel Index Katz Activities of Daily Living (ADL) Lawton Instrumental Activities of Daily Living (IADL) More sophisticated testing includes giving a person a medicine bottle and asking them how they would take the medicines, opening and shutting a variety of small doors, putting beans in a tin can, putting on a jacket or buttoning a shirt Social Activities Inventory
Hearing	Do you have trouble hearing especially in a noisy environment?	Hearing Handicap Inventory for the Elderly Audioscope Remove wax Consider hearing frequency testing
Incontinence	Do you wet yourself?	Urine for cells and culture Does it occur when coughing, sneezing (stress) Do you get the urge to go and have to go immediately (urge) Urodynamics
Insomnia	Do you have trouble sleeping? Are you tired during the day? Does your partner say that you stop breathing when sleeping?	Full sleep history including daytime napping, pain at night, nocturia, time going to sleep and environment Consider overnight sleep test for sleep apnoea

Dimension	Screening test	Assessment tests
Masked renal failure	Loss of muscle mass leads to normal serum creatinine levels in the face of severe renal failure	Use Cockcroft–Gault formula or measure serum cystatin-C
Memory	Do you have problems remembering anything or do any of your family or friends think you are having problems?	Saint Louis University/VA Mental Status Examination (SLUMS) If positive, TSH, vitamin B_{12} and homocysteine Consider MRI in some cases
Mobility/balance	Do you have trouble walking or lose your balance? Have you had a fall? Do you have a fear of falling?	Get up and go from a chair (may ask to do so holding a glass of water) Gait speed over 10 metres Stand on one foot with eyes open and shut Observe walking with a turn or dance with the patient. This should also be done while distracting the patient Measure stride length and variability
Nutrition	Have you lost weight? Height? Weight? Simplified Nutrition Assessment Questionnaire (SNAQ)	Body mass index Mini nutritional assessment Use 'meals on wheels' mnemonic to look for treatable causes
Osteoporosis	What was your height when 25 years old? Compared it with measured height now	Bone mineral density All women should have first at 50 years and men by 65 years of age. If results are borderline it should be repeated in 2 years during the same season 25-OH-vitamin D levels should be greater than 30 mg dl^{-1} All persons with a hip fracture should have calcium, vitamin D and bisphosphonates, unless a contraindication, e.g. renal failure
Pain	Do you hurt? Does your medicine relieve your pain?	Pain scale (faces better than Likert Scale) Full pain history If muscle pain, check ESR for polymyalgia rheumatica If temporal headache, check neck muscles for cramping
Polypharmacy	Are you on 7 or more medications? Is the person on any inappropriate medicines using the Beers Criteria?	Add history of herbal and over-the-counter medications Ask why they are taking all medications, are they compliant, who prescribed them and are there any side effects Check for orthostasis
Prostate	Do you have difficulty initiating your urine stream or dribble afterwards?	International Prostate Symptom Score Rectal examination Prostate-specific antigen
Sexuality	Are you having sexual relations? Do you want to have sex? How is your sexual desire? Then only; are you impotent?	*For women:* Ask about dyspareuria (pain on intercourse) Poor vaginal lubrication, itching or burning Are intimacy needs being met? *For men:* ADAM Questionnaire for low testosterone; if positive, bioavailable testosterone

(*continued overleaf*)

Dimension	Screening test	Assessment tests
		Discuss erectile dysfunction, including soft erections *For both:* Does their partner's or their health cause sexual difficulty? Are they using appropriate protection from sexually transmitted diseases?
Skin assessment	Do you have any new sores, rashes or growths on your body? Are you itching? Are any of your moles growing?	Full body examination Braden Scale to determine risk of pressure ulcers
Social support	Who lives with you? Who helps you?	Older American Resources and Services OARS Social Resources Scale explores fully the available helpers and strength of relationships
Spells	Do you have spells? Have you fainted (lost consciousness)? Have you fallen recently?	Orthostasis (if present, BUN, glucose, creatinine, sodium, haemoglobin) Carotid sinus massage Echocardiography Event monitor EKG Consider partial complex seizures (often missed in the elderly) and if likely need EEG
Vaccinations	Have you been vaccinated for flu, pneumonia and tetanus?	Influenza – yearly Pneumonia – every 5 years Tetanus – every 10 years Herpes zoster – once
Vision	Do you have trouble seeing?	Snellen eye chart Useful field of vision Dark adaptation Fundus examination

Activities of daily living (ADLs) and instrumental activities of daily living (IADLs)

Basic ADLs	IADLs
Bathing	Using the telephone
Dressing	Shopping
Toileting	Food preparation
Transfers	Housekeeping
Continence	Laundry
Feeding	Transportation
	Taking medicine
	Managing money
ADL Score:____/6	IADL Score:____/8

Dental

Screening assessment for dental conditions that may interfere with proper nutritional intake and possibly dispose a person to involuntary weight loss.

Dry mouth (2 points)
Eating difficulty (1 point)
No recent dental care (1 point) (within 2 years)
Tooth or mouth pain (2 points)
Alterations or change in food selection (1 point)
Lesions, sores or lumps in mouth (2 points)

A score of ≥3 points could indicate dental problems. Patient may need evaluation by a dentist.

Hallpike Manoeuvre

With the patient sitting, turn their head to 45° on one side. Hold the head at this angle while rapidly lowering the

patient so that their head is 30° below the level of the examining table. Watch for nystagmus that comes on a few seconds after lowering them; lasts less than 30 seconds and decreases with repeated testing. Also ask if their symptoms are reproducible.

Osler Manoeuvre for pseudohypertension

Pump the blood pressure cuff up until you can no longer feel the pulse. Run your finger along the artery. At this stage it should have collapsed. If you can still feel the artery this is suggestive of arteriosclerosis and pseudohypertension.

Simplified Nutrition Assessment Questionnaire (SNAQ)

1 My appetite is
- A very poor
- B poor
- C average
- D good
- E very good

2 When I eat
- A I feel full after eating only a few mouthfuls
- B I feel full after eating about one-third of a meal
- C I feel full after eating over half of a meal
- D I feel full after eating most of the meal
- E I hardly ever feel full

3 Food tastes
- A very bad
- B bad
- C average
- D good
- E very good

4 Normally I eat
- A less than one meal a day
- B one meal a day
- C two meals a day
- D three meals a day
- E more than 3 meals a day

Instructions: Complete the questionnaire by circling the correct answers and then tally the results based upon the following numerical scale: A = 1, B = 2, C = 3, D = 4, E = 5.
Scoring: If the score is less than 14, there is a significant risk of weight loss.

The Mini-Nutritional Assessment (MNA) Scale

Last name: _____ First name: _____ Sex: _____ Date: _____

Age: _____ Weight, kg: _____ Height, cm: _____ I.D. Number: _____

Complete the screen by filling in the boxes with the appropriate numbers.
Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe loss of appetite
1 = moderate loss of appetite
2 = no loss of appetite ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3 kg (6.6 lbs)
1 = does not know
2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed/chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F Body Mass Index (BMI) (weight in kg) / (height in m)^2
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

Screening score (subtotal max. 14 points) ☐☐
12 points or greater Normal – not at risk – no need to complete assessment
11 points or below Possible malnutrition – continue assessment

Assessment

G Lives independently (not in a nursing home or hospital)
0 = no 1 = yes ☐

H Takes more than 3 prescription drugs per day
0 = yes 1 = no ☐

I Pressure sores or skin ulcers
0 = yes 1 = no ☐

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals ☐

K Selected consumption markers for protein intake
- At least one serving of dairy products (milk, cheese, yogurt) per day? yes ☐ no ☐
- Two or more servings of legumes or eggs per week? yes ☐ no ☐
- Meat, fish or poultry every day yes ☐ no ☐

0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes ☐.☐

L Consumes two or more servings of fruits or vegetables per day?
0 = no 1 = yes ☐

M How much fluid (water, juice, coffee, tea, milk…) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups ☐.☐

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem ☐

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem ☐

P In comparison with other people of the same age, how do they consider their health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better ☐.☐

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC 22 or greater ☐.☐

R Calf circumference (CC) in cm
0 = CC less than 31 1 = CC 31 or greater ☐

Assessment (max. 16 points) ☐☐.☐
Screening score ☐☐
Total Assessment (max. 30 points) ☐☐.☐

Malnutrition Indicator Score
17 to 23.5 points at risk of malnutrition ☐
Less than 17 points malnourished ☐

Saint Louis University social activities assessment

1 How often do you go out socially?
- **a** daily
- **b** twice a week or more
- **c** weekly
- **d** monthly
- **e** rarely

2 How often do you garden?
- **a** at least an hour daily
- **b** less than an hour daily
- **c** twice a week or more
- **d** weekly
- **e** rarely

3 How often do you go to church/synagogue/mosque?
- **a** more than once a week
- **b** weekly
- **c** at least once a month
- **d** only on religious holidays
- **e** never

4 How often do you talk to friends or family on the telephone?
- **a** more than once a day
- **b** daily
- **c** 2 to 4 times a week
- **d** weekly
- **e** rarely

5 How often do you go to a restaurant to eat?
- **a** daily
- **b** twice a week or more
- **c** weekly
- **d** monthly
- **e** rarely

6 How often do you go for a walk?
- **a** daily
- **b** twice a week or more
- **c** weekly
- **d** monthly
- **e** rarely

7 How often do you go dancing?
- **a** daily
- **b** twice a week or more
- **c** weekly
- **d** monthly
- **e** rarely

8 How often do you go to a concert/theatre/movie?
- **a** daily
- **b** twice a week or more
- **c** weekly
- **d** monthly
- **e** rarely

9 How often do you play with your grandchildren?
- **a** daily
- **b** twice a week or more
- **c** weekly
- **d** monthly
- **e** rarely

10 How satisfied are you with the time spent and quality of your social activities?
- **a** extremely satisfied
- **b** very satisfied
- **c** satisfied
- **d** somewhat satisfied
- **e** not at all satisfied

The Confusion Assessment Method (CAM) diagnostic algorithm

The diagnosis of delirium by the Confusion Assessment Method (CAM) requires the presence of features 1 and 2 plus either 3 or 4.

Feature 1: *Acute onset and fluctuating course*. This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behaviour fluctuate during the day, that is, tend to come and go or increase and decrease in severity?
Check appropriate box: Present ☐ Absent ☐

Feature 2: *Inattention*. This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?
Check appropriate box: Present ☐ Absent ☐

Feature 3: *Disorganized thinking*. This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas or unpredictable switching from subject to subject?
Check appropriate box Present ☐ Absent ☐

Feature 4: *Altered level of consciousness*. This feature is shown by an answer other than 'alert' to the following question: Overall, how would you rate this patient's level of consciousness? Alert (normal); Vigilant (hyperalert overly sensitive to environmental stimuli, startled very easily); Lethargic (drowsy, easily aroused); Stupor (difficult to arouse); Coma (unarousable); Uncertain
Check appropriate box Present ☐ Absent ☐

Type of delirium
Hyperalert ☐ Hypoalert ☐ Mixed ☐

Reference: Inouye S, van Dyck C, Alessi C *et al*. Clarifying confusion: the confusion assessment method. *Ann Intern Med* 1990;**113**:941–8.

Saint Louis University

Mental Status (SLUMS) Examination

Name _____ Age _____

Is patient alert? _____ Level of education _____

__/1 ❶ **1. What day of the week is it?**

__/1 ❶ **2. What is the year?**

__/1 ❶ **3. What state are we in?**

4. Please remember these five objects. I will ask you what they are later.

Apple Pen Tie House Car

5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.

❶ **How much did you spend?**

__/3 ❷ **How much do you have left?**

6. Please name as many animals as you can in one minute.

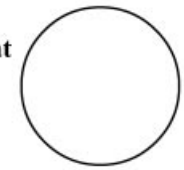
__/3 ❶ 0-4 animals ❶ 5-9 animals ❷ 10-14 animals ❸ 15+ animals

__/5 **7. What were the five objects I asked you to remember?** 1 point for each one correct.

8. I am going to give you a series of numbers and I would like you to give them to me backwards. For example, if I say 42, you would say 24.

__/2 ❶ 87 ❶ 649 ❶ 8537

9. This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o'clock.



❷ Hour markers okay

__/4 ❷ Time correct

__/2 ❶ **10. Please place an X in the triangle.**

❶ **Which of the above figures is largest?**

11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.

Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.

❷ **What was the female's name?** ❷ **What work did she do?**

__/8 ❷ **When did she go back to work?** ❷ **What state did she live in?**

_____ **TOTAL SCORE**

Department of Veterans Affairs

SAINT LOUIS UNIVERSITY

AGING SUCCESSFULLY

SCORING		
HIGH SCHOOL EDUCATION		LESS THAN HIGH SCHOOL EDUCATION
27-30	Normal	20-30
20-26	MCI	15-19
1-19	Dementia	1-14

WA Banks and JE Morley. Memories are made of this: Recent advances in understanding, cognitive impairment, and dementia. *J Gerontol Med Sci* 2003;58A:314-21.

Saint Louis University Division of Geriatrics

Passport to Aging Successfully*

SAINT LOUIS UNIVERSITY

Please complete this questionnaire before seeing your physician and take it with you when you go.

NAME _____ **AGE** _____

BLOOD PRESSURE laying down: _____ standing: _____

WEIGHT now: _____ 6 months ago: _____ change: _____

HEIGHT at age 20: _____ now: _____

CHOLESTEROL LDL: _____ HDL: _____

VACCINATIONS ☐Influenza (yearly) ☐Pneumococcal ☐Tetanus (every 10 years)

TSH Date: _____ **FASTING GLUCOSE** Date: _____

Do you SMOKE? _____

How much ALCOHOL do you drink? _____ per day

Do you use your SEATBELT? _____

Do you chew TOBACCO? _____

EXERCISE: How often do you...

do endurance exercises (walk briskly 20 to 30 minutes/day or climb 10 flights of stairs) _____ /week

do resistance exercises? _____ /week do balance exercises? _____ /week

do posture exercises? _____ /week do flexibility exercises? _____ /week

Can you SEE ADEQUATELY in poor light? _____

Can you HEAR in a noisy environment? _____

Are you INCONTINENT? _____

Have you a LIVING WILL or durable POWER OF ATTORNEY FOR HEALTH? _____

Do you take ASPIRIN daily (only if you have had a heart attack or have diabetes)? _____

Do you have any concerns about your PERSONAL SAFETY? _____

When did you last have your STOOL TESTED for blood? _____

When were you last screened for OSTEOPOROSIS? _____

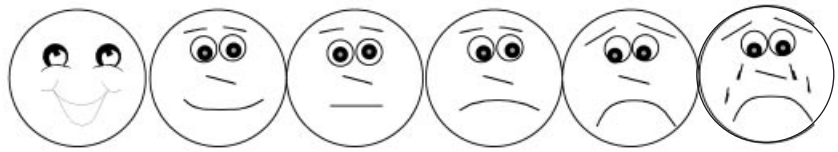
Are you having trouble REMEMBERING THINGS? _____

Do you have enough FOOD? _____

Are you SAD? _____

Do you have PAIN? _____

If so, which face best describes your pain?



MALES

Do you have trouble passing urine? _____

Have you discussed PSA testing with your doctor? _____

What is your ADAM score? _____

FEMALES

When was your last pap smear? _____

When was your last mammogram? _____

Do you check your breasts monthly? _____

Are you satisfied with your sex life? _____

Now, please answer the four questionnaires on the next page.

* This questionnaire is based on the health promotion and prevention guidelines developed by Gerimed® and Saint Louis University Division of Geriatric Medicine.

Passport to Aging Successfully

Please fill out these forms before seeing your physician and take them with you when you go.

Geriatric Depression Scale	**(circle one)**
Are you basically satisfied with your life?	YES NO
Have you dropped many of your activities and interests?	YES NO
Do you feel that your life is empty?	YES NO
Do you often get bored?	YES NO
Are you in good spirits most of the time?	YES NO
Are you afraid that something bad is going to happen to you?	YES NO
Do you feel happy most of the time?	YES NO
Do you often feel helpless?	YES NO
Do you prefer to stay at home, rather than going out and doing new things?	YES NO
Do you feel you have more problems with memory than most?	YES NO
Do you think it is wonderful to be alive?	YES NO
Do you feel pretty worthless the way you are now?	YES NO
Do you feel full of energy?	YES NO
Do you feel that your situation is hopeless?	YES NO
Do you think that most people are better off than you are?	YES NO

Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist* 1986;5:165.

CAGE

Have you ever considered **C**utting down on your alcohol intake? _____

Do people **A**nnoy you by criticizing your drinking? _____

Have you ever felt bad or **G**uilty about your drinking? _____

Have you ever had an alcoholic drink first thing in the morning (**E**yeopener) to steady your nerves or get rid of a hangover? _____

ADAM (Men only)

1. Do you have a decrease in libido? _____
2. Do you have a lack of energy? _____
3. Do you have a decrease in strength and/or endurance? _____
4. Do you have a decreased enjoyment of life? _____
5. Are you sad? _____
6. Are you grumpy? _____
7. Are your erections less strong? _____
8. Have you noticed a recent deterioration in your ability to play sports? _____
9. Are you falling asleep earlier after dinner? _____
10. Has there been a recent deterioration in your work performance? _____

Epworth Sleepiness Questionnaire

How likely are you to doze off or to fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Use the following scale to choose the most appropriate number for each situation.

0–would never doze	1–slight chance of dozing
2–moderate chance of dozing	3–high chance of dozing

Situation	**Chance of dozing**
Sitting and reading	
Watching TV	
Sitting inactive in a public place	
As a passenger in a car for an hour	
Lying down to rest in the afternoon	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car while stopped for a few minutes	
Total	___ / 24

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